Amendments to the Specification:

In the Sequence Listing:

Please add new pages 1 to12, containing the sequence listing.

On page 1, line 5 of the application, please insert:

--CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims benefit of U.S. Provisional Application 60/253,324, filed November 27, 2000, and incorporated herein by reference.--

Please replace the paragraphs on page 33, l. 29 to page 36, l. 4, with the following rewritten paragraph:

--[20] In another embodiment, the invention describes a method according to any one of embodiments [9]-[12], [16] and [19], wherein the radiopharmaceutical is selected from the group:

^{99m}Tc(tricine)(TPPTS)(cyclo(Arg-Gly-Asp-D-Tyr(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-3-aminopropyl)-Val)), SEQ ID NO: 1;

^{99m}Tc(tricine)(TPPMS)(cyclo(Arg-D-Val-D-Tyr(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-3-aminopropyl)-D-Asp-Gly)), SEQ ID NO: 2;

^{99m}Tc(tricine)(TPPDS)(cyclo(Arg-D-Val-D-Tyr(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-3-aminopropyl)-D-Asp-Gly)), SEQ ID NO: 2;

^{99m}Tc(tricine)(TPPTS)(cyclo(Arg-D-Val-D-Tyr(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-3-aminopropyl)-D-Asp-Gly)), SEQ ID NO: 2;

^{99m}Tc(tricine)(TPPTS)(cyclo(Arg-Gly-Asp-D-Phe-Lys(N-[[5-[carbonyl]-2-pyridinyl]diazenido]))), SEQ ID NO: 3;

^{99m}Tc(tricine)(TPPTS)(cyclo(Arg-Gly-Asp-D-Tyr-Lys(N-[[5-[carbonyl]-2-pyridinyl]diazenido]))), SEQ ID NO: 4;

^{99m}Tc(tricine)(TPPTS)([[5-[carbonyl]-2-pyridinyl]diazenido]-Phe-Glu(cyclo{Lys-Arg-Gly-Asp-D-Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe}), SEQ ID NO: 5;

^{99m}Tc(tricine)(TPPTS)(cyclo{Arg-Gly-Asp-D-Nal-Lys([[5-[carbonyl]-2-pyridinyl]diazenido])}), SEQ ID NO: 6;

^{99m}Tc(tricine)(TPPTS)([[5-[carbonyl]-2-pyridinyl]-diazenido]-Glu(cyclo{Lys-Arg-Gly-Asp-D-Nal})-cyclo{Lys-Arg-Gly-Asp-D-Nal}), SEQ ID NO: 7;

^{99m}Tc(tricine)(TPPTS)(cyclo(Arg-Gly-Asp-D-Tyr((N-[[5-[carbonyl]-2-pyridinyl]diazenido]-18-amino-14-aza-4,7,10-oxy-15-oxo-octadecoyl)-3-aminopropyl)-Val)), SEQ ID NO: 1;

^{99m}Tc(tricine)(TPPTS)(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-Glu(O-cyclo(Lys-Arg-Gly-Asp-D-Phe))-O-cyclo(Lys-Arg-Gly-Asp-D-Phe)), SEQ ID NO: 8;

^{99m}Tc(tricine)(TPPTS)(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-Glu(O-cyclo(D-Tyr(3-aminopropyl)-Val-Arg-Gly-Asp))-O-cyclo(D-Tyr(3-aminopropyl)-Val-Arg-Gly-Asp)), SEQ ID NO: 9;

^{99m}Tc(tricine)(TPPTS)(cyclo(Arg-Gly-Asp-Lys(N-[[5-[carbonyl]-2-pyridinyl]diazenido])-D-Val)), SEQ ID NO: 10;

^{99m}Tc(tricine)(TPPTS)(cyclo{D-Lys([[5-[carbonyl]-2-pyridinyl]diazenido])-D-Phe-D-Asp-Gly-Arg}), SEQ ID NO: 11;

^{99m}Tc(tricine)(TPPTS)([[5-[carbonyl]-2-pyridinyl]diazenido]-Glu(cyclo{D-Lys-D-Phe-D-Asp-Gly-Arg})-cyclo{D-Lys-D-Phe-D-Asp-Gly-Arg}), SEQ ID NO: 12;

^{99m}Tc(tricine)(TPPTS)(cyclo{D-Phe-D-Lys([[5-[carbonyl]-2-pyridinyl]diazenido])-D-Asp-Gly-Arg}), SEQ ID NO: 13;

^{99m}Tc(tricine)(TPPTS)(cyclo(N-Me-Arg-Gly-Asp-ATA-D-Lys(N-[[5-[carbonyl]-2-pyridinyl]diazenido]))), SEQ ID NO: 14;

^{99m}Tc(tricine)(TPPTS)(cyclo{Cit-Gly-Asp-D-Phe-Lys([[5-[carbonyl]-2-pyridinyl]diazenido])}), SEQ ID NO: 15; and

^{99m}Tc(tricine)(1,2,4-triazole)(cyclo(Arg-Gly-Asp-D-Tyr(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-3-aminopropyl)-Val)), SEQ ID NO: 1.--

Please replace the paragraphs on page 36, l. 11-20 with the following rewritten paragraph:

--[22] In another embodiment, the invention describes a method according to embodiment [21], wherein the radiopharmaceutical is selected from the group:

(DOTA-^{111}In)-Glu(cyclo{Lys-Arg-Gly-Asp-D-Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe}, SEQ ID NO: 8;

cyclo(Arg-Gly-Asp-D-Phe-Lys(DTPA-^{111}In)), SEQ ID NO: 3; and,

cyclo(Arg-Gly-Asp-D-Phe-Lys)$_2$(DTPA-^{111}In), SEQ ID NO: 3. –

Please replace the paragraphs on page 37, l. 14-18 with the following rewritten paragraph:

--[28] In another embodiment, the invention describes a method according to embodiment [27], wherein the contrast agent is:

cyclo(Arg-Gly-Asp-D-Tyr(N-DTPA(Gd(III))-3-aminopropyl)-Val), SEQ ID NO: 1.--

Please replace the paragraphs on page 51, l. 1-14 with the following rewritten paragraph:

--[42] In another embodiment, the invention describes a method according to any one of embodiments [39]-[41], wherein the compound is selected from the group:

1-(1,2-Dipalmitoyl-sn-glycero-3-phosphoethanolamino)-12-(cyclo(Arg-Gly-Asp-D-Phe-Lys)-dodecane-1,12-dione, SEQ ID NO: 3;

1-(1,2-Dipalmitoyl-sn-glycero-3-phosphoethanolamino)-12-((ω-amino-PEG$_{3400}$-α-carbonyl)-cyclo(Arg-Gly-Asp-D-Phe-Lys))-dodecane-1,12-dione, SEQ ID NO: 3; and

1-(1,2-Dipalmitoyl-sn-glycero-3-phosphoethanolamino)-12-((ω-amino-PEG$_{3400}$-α-carbonyl)-Glu-(cyclo(Arg-Gly-Asp-D-Phe-Lys))$_2$)-Dodecane-1,12-dione, SEQ ID NO: 16.--

Please replace the paragraphs on page 59, l. 27 to page 60, l. 17 with the following rewritten paragraphs:

--In another embodiment, the metallopharmaceutical is a therapeutic radiopharmaceutical selected from the group: cyclo(Arg-Gly-Asp-D-Phe-Lys(DTPA-^{153}Sm)), SEQ ID NO: 3; cyclo(Arg-Gly-Asp-D-Phe-Lys)$_2$(DTPA-^{153}Sm), SEQ ID NO: 3; and, cyclo(Arg-Gly-Asp-D-Tyr(N-DTPA(^{153}Sm)-3-aminopropyl)-Val), SEQ ID NO: 1.

In another embodiment, the metallopharmaceutical is a therapeutic radiopharmaceutical and the radioisotope is ^{177}Lu.

In another embodiment, the metallopharmaceutical is a therapeutic radiopharmaceutical selected from the group: cyclo(Arg-Gly-Asp-D-Phe-Lys(DTPA-^{177}Lu)), SEQ ID NO: 3; (DOTA-^{177}Lu)-Glu(cyclo{Lys-Arg-Gly-Asp-D-Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe}, SEQ ID NO: 8; cyclo(Arg-Gly-Asp-D-Phe-Lys)$_2$(DTPA-^{177}Lu), SEQ ID NO: 3; and, cyclo(Arg-Gly-Asp-D-Tyr(N-DTPA(^{177}Lu)-3-aminopropyl)-Val), SEQ ID NO: 1.

In another embodiment, the metallopharmaceutical is a therapeutic radiopharmaceutical and the radioisotope is ^{90}Y.

In another embodiment, the metallopharmaceutical is a therapeutic radiopharmaceutical of formula (DOTA-^{90}Y)-Glu(cyclo{Lys-Arg-Gly-Asp-D-Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe}, SEQ ID NO: 8.--

Please replace the paragraphs on page 82, l. 30 to page 84, l. 21 with the following rewritten paragraphs:

--The pharmaceuticals of the present invention are comprised of a targeting moiety for a receptor that is expressed or upregulated in angiogenic tumor vasculature. For targeting the VEGF receptors, Flk-1/KDR, Flt-1, and neuropilin-1, the targeting moieties are comprised of peptides or peptidomimetics that bind with high affinity to the receptors. For example, peptides comprised of a 23 amino acid portion of the C-terminal domain of VEGF have been synthesized which competitively inhibit binding of VEGF to VEGFR (Soker, et. al., J. Biol. Chem., 1997, 272, 31582-8). Linear peptides of 11 to 23 amino acid residues that bind to the basic FGF receptor (bFGFR) are described by Cosic et. al., Mol. and Cell. Biochem., 1994, 130, 1-9. A preferred linear peptide antagonist of the bFGFR is the 16 amino acid peptide, Met-Trp-Tyr-Arg-Pro-Asp-Leu-Asp-Glu-Arg-Lys-Gln-Gln-Lys-Arg-Glu, SEQ ID NO: 26. Gho et. al. (Cancer Research, 1997, 57, 3733-40) describe the identification of small peptides that bind with high affinity to the angiogenin receptor on the surface of endothelial cells. A preferred peptide is Ala-Gln-Leu-Ala-Gly-Glu-Cys-Arg-Glu-Asn-Val-Cys-Met-Gly-Ile-Glu-Gly-Arg, SEQ ID NO: 27, in which the two Cys residues form an intramolecular disulfide bond. Yayon et. al. (Proc. Natl. Acad. Sci, USA, 1993, 90, 10643-7) describe other linear peptide antagonists of FGFR, identified from a random phage-displayed peptide library. Two linear octapeptides, Ala-Pro-Ser-Gly-His-Tyr-Lys-Gly, SEQ ID NO: 28, and Lys-Arg-Thr-Gly-Gln-Tyr-Lys-Leu, SEQ ID NO: 45, are preferred for inhibiting binding of bFGF to it receptor.

Targeting moieties for integrins expressed in tumor vasculature include peptides and peptidomimetics that bind to $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_5\beta_1$, $\alpha_4\beta_1$, $\alpha_1\beta_1$, and $\alpha_2\beta_2$. Pierschbacher and Rouslahti (J.

Biol. Chem., 1987, 262, 17294-8) describe peptides that bind selectively to $\alpha 5\beta 1$ and $\alpha_V\beta 3$. U.S. 5,536,814 describe peptides that bind with high affinity to the integrin $\alpha 5\beta 1$. Burgess and Lim (J. Med. Chem., 1996, 39, 4520-6) disclose the synthesis three peptides that bind with high affinity to $\alpha_V\beta 3$: cyclo[Arg-Gly-Asp-Arg-Gly-Asp], SEQ ID NO: 29, cyclo[Arg-Gly-Asp-Arg-Gly-D-Asp], SEQ ID NO: 29, and the linear peptide Arg-Gly-Asp-Arg-Gly-Asp, SEQ ID NO: 29. U.S. 5,770,565 and U.S. 5,766,591 disclose peptides that bind with high affinity to $\alpha_V\beta 3$. U.S. 5,767,071 and U.S. 5,780,426, disclose cyclic peptides that have an exocyclic Arg amino acid that have high affinity for $\alpha_V\beta 3$. Srivatsa et. al., (Cardiovascular Res., 1997, 36, 408-28) describe the cyclic peptide antagonist for $\alpha_V\beta 3$, cyclo[Ala-Arg-Gly-Asp-Mamb]. Tran et. al., (Bioorg. Med. Chem. Lett., 1997, 7, 997-1002) disclose the cyclic peptide cyclo[Arg-Gly-Asp-Val-Gly-Ser-BTD-Ser-Gly-Val-Ala], SEQ ID NO: 46, that binds with high affinity to $\alpha_V\beta 3$. Arap et. al. (Science, 1998, 279, 377-80) describe cyclic peptides that bind to $\alpha_V\beta 3$ and $\alpha_V\beta 5$, Cys-Asp-Cys-Arg-Gly-Asp-Cys-Phe-Cys, SEQ ID NO: 47, and cyclo[Cys-Asn-Gly-Asp-Cys], SEQ ID NO: 48. Corbett et. al. (Biorg. Med. Chem. Lett., 1997, 7, 1371-6) describe a series of $\alpha_V\beta 3$ selective peptidomimetics. And Haubner et. al., (Angew. Chem. Int. Ed. Engl., 1997, 36, 1374-89) disclose peptides and peptidomimetic $\alpha_V\beta 3$ antagonists obtained from peptide libraries.--

Please replace the paragraphs on page 126, l. 6-8 with the following rewritten paragraph:

--Synthesis of cyclo{Arg-Gly-Asp-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-Val}, SEQ ID NO: 1--

Please replace the paragraphs on page 126, l. 11 to page 127, l. 9 with the following rewritten paragraphs:

-- Part A: Preparation of cyclo{Arg(Tos)-Gly-Asp(OBzl)-D-Tyr(N-Cbz-3-aminopropyl)-Val}, SEQ ID NO: 1.

The N-terminus Boc- protecting group of the peptide sequence Boc-Asp(OBzl)-D-Tyr(N-Cbz-aminopropyl)-Val-Arg(Tos)-Gly-Oxime, SEQ ID NO. 49, resin was removed using standard deprotection (25% TFA in CH_2Cl_2). After eight washes with DCM, the resin was treated with 10% DIEA/DCM (2 x 10 min.). The resin was subsequently washed with DCM (x 5) and dried under high vacuum. The resin (1.7474 g, 0.55 mmol/g) was then suspended in dimethylformamide (15 mL). Glacial acetic acid (55.0 μL, 0.961 mmol) was added, and the reaction mixture was heated at 50 °C for 72 h. The resin was filtered, and washed with DMF (2 x 10 mL). The filtrate was concentrated to an oil under high vacuum. The resulting oil was triturated with ethyl acetate. The solid thus obtained was filtered, washed with ethyl acetate, and dried under high vacuum to give 444.4 mg of the desired product. ESMS: Calcd. for $C_{51}H_{63}N_9O_{12}S$, 1025.43; Found, 1026.6 [M+H]+1. Analytical HPLC, Method 1A, R_t = 14.366 min, Purity = 75%.

Part B: Preparation of cyclo{Arg-Gly-Asp-D-Tyr(3-aminopropyl)-Val}, SEQ ID NO: 1; Trifluoroacetic acid salt.--

Please replace the paragraphs on page 127, l. 13 to page 128, l. 2 with the following rewritten paragraph:

--Cyclo{Arg(Tos)-Gly-Asp(OBzl)-D-Tyr(N-Cbz-3-aminopropyl)-Val}, SEQ ID NO: 1 (0.150 g, 0.146 mmol) was dissolved in trifluoroacetic acid (0.6 mL) and cooled to -10 °C. Trifluoromethanesulfonic acid (0.5 mL) was added dropwise,

maintaining the temperature at -10 °C. Anisole (0.1 mL) was added and the reaction mixture was stirred at -10 °C for 3 h. Diethyl ether was added, the reaction mixture cooled to -35 °C and then stirred for 30 min. The reaction mixture was cooled further to -50 °C and stirred for 30 min. The crude product obtained was filtered, washed with diethyl ether, dried under high vacuum, and purified by preparative HPLC Method 1, to give 29.7 mg (23%) of the desired product as a lyophilized solid. ESMS: Calcd. for $C_{29}H_{45}N_9O_8$, 647.34; Found, 648.5 [M+H]+1. Analytical HPLC, Method 1B, R_t = 10.432 min, Purity = 91%.--

Please replace the paragraphs on page 128, l. 19 to page 129, l. 9 with the following rewritten paragraphs:

-- Part C. Preparation of cyclo{Arg-Gly-Asp-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-Val}, SEQ ID NO: 1.

Cyclo{Arg-Gly-Asp-D-Tyr(3-aminopropyl)-Val}, SEQ ID NO: 1, trifluoroacetic acid salt (0.020 g, 0.0228 mmol) was dissolved in DMF (1 mL). Triethylamine (9.5 μL, 0.0648 mmol) was added, and after 5 min of stirring 2-[[[5-[[(2,5-dioxo-1-pyrrolidinyl)oxy]carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid, monosodium salt (0.0121 g, 0.0274 mmol) was added. The reaction mixture was stirred for 7 days, and then concentrated to an oil under high vacuum. The oil was purified by preparative HPLC Method 1 to give 8.9 mg (37%) of the title product as a lyophilized solid (TFA salt). HRMS: Calcd. for $C_{42}H_{54}N_{12}O_{12}S$ +H, 951.3783; Found, 951.3767. Analytical HPLC, Method 1B, R_t = 14.317 min, Purity = 95%.

Example 2

Synthesis of cyclo{Arg-Gly-Asp-D-Tyr((N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-18-amino-14-aza-4,7,10-oxy-15-oxo-octadecoyl)-3-aminopropyl)-Val}, SEQ ID NO: 1--

Please replace the paragraphs on page 131, l. 5-7 with the following rewritten paragraph:

--Part C. Preparation of cyclo{Arg-Gly-Asp-D-Tyr(3-(3-(N-(3-(2-(2-(3-((tert-butoxy)-carbonylamino)propoxy)ethoxy)-ethoxy)propyl)carbamoyl)-propanamido)propyl)-Val}, SEQ ID NO: 1.--

Please replace the paragraphs on page 131, l. 13 to page 133, l. 14 with the following rewritten paragraphs:

--Cyclo{Arg-Gly-Asp-D-Tyr(3-aminopropyl)-Val}, SEQ ID NO: 1, TFA salt (0.040 g, 0.0457 mmol) was dissolved in DMF (2 mL). Triethylamine (19.1 μL, 0.137 mmol) was added and after stirring for 5 minutes 3-(N-(3-(2-(2-(3-((tert-butoxy)-carbonylamino)propoxy)ethoxy)ethoxy)propyl)carbamoyl)propanoic acid succinimide ester (0.0284 g, 0.0548 mmol) was added. The reaction mixture was stirred under N_2 for 48 h and then concentrated to an oil under high vacuum. The oil was triturated with ethyl acetate, the product filtered, washed with ethyl acetate, and dried under high vacuum. The crude product was purified by Preparative HPLC Method 1 to give 7.4 mg (14%) of the desired product as a lyophilized solid. ESMS: Calcd. for $C_{48}H_{79}N_{11}O_{15}$, 1049.58; Found, 1050.5 [M+H]+1. Analytical HPLC, Method 1B, R_t = 20.417 min, Purity = 100%.

Part D. Preparation of cyclo{Arg-Gly-Asp-D-Tyr(3-(3-(N-(3-(2-(2-(3-(amino)propoxy)ethoxy)ethoxy)propyl)carbamoyl)-propanamido)propyl)-Val}, SEQ ID NO: 1.

Cyclo{Arg-Gly-Asp-D-Tyr(3-(3-(N-(3-(2-(2-(3-((tert-butoxy)-carbonylamino)propoxy)ethoxy)ethoxy)propyl)-carbamoyl)-propanamido)propyl)-Val}, SEQ ID NO: 1, (6.0 mg, 0.00515 mmol) was dissolved in methylene chloride (1 mL) and trifluoroacetic acid (1 mL) was added. The solution stirred for 2 h and then concentrated to an oil under high vacuum. The oil was triturated with diethyl ether, the product filtered, washed with diethyl ether, and dried under high vacuum to give 6.0 mg (98%) of the desired product. ESMS: Calcd. for $C_{43}H_{71}N_{11}O_{13}$, 949.52; Found, 950.6 [M+H]+1. Analytical HPLC, Method 1B, R_t = 14.821 min, Purity = 73%.

Part E. Preparation of cyclo{Arg-Gly-Asp-D-Tyr((N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-18-amino-14-aza-4,7,10-oxy-15-oxo-octadecoyl)-3-aminopropyl)-Val}, SEQ ID NO: 1.

Cyclo{Arg-Gly-Asp-D-Tyr(3-(3-(N-(3-(2-(2-(3-(amino)propoxy)ethoxy)ethoxy)propyl)carbamoyl)-propanamido)propyl)-Val}, SEQ ID NO: 1, (5.0 mg, 0.00424 mmol) was dissolved in dimethylformamide (1 mL). Triethylamine (1.8 μL, 0.0127 mmol) was added, and after stirring for 5 min 2-[[[5-[[(2,5-dioxo-1-pyrrolidinyl)oxy]-carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid, monosodium salt (2.2 mg, 0.00509 mmol) was added. The reaction mixture was stirred for 24 h and then concentrated to an oil under high vacuum. The oil was purified by preparative HPLC Method 1 to give 2.2 mg (38%) of the desired product as a lyophilized solid (TFA salt). ESMS: Calcd. for $C_{56}H_{80}N_{14}O_{17}S$, 1252.6;

Found, 1253.7 ($M+H^+$). Analytical HPLC, Method 1B, R_t = =17.328 min, Purity = 100%.

Example 3

Synthesis of [2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-Glu(cyclo{D-Tyr(3-aminopropyl)-Val-Arg-Gly-Asp})-cyclo{D-Tyr(3-aminopropyl)-Val-Arg-Gly-Asp}, SEQ ID NO: 9--

Please replace the paragraphs on page 133, l. 18 to page 134, l. 11 with the following rewritten paragraphs:

--Part A. Preparation of Boc-Glu(cyclo{D-Tyr(3-aminopropyl)-Val-Arg-Gly-Asp})-cyclo{D-Tyr(3-aminopropyl)-Val-Arg-Gly-Asp}, SEQ ID NO: 9.

Cyclo{D-Tyr(3-aminopropyl)-Val-Arg-Gly-Asp}, SEQ ID NO: 19, (0.040 g, 0.0457 mmol) was dissolved in dimethylformamide (2 mL). Triethylamine (19.1 μL, 0.137 mmol) was added and the reaction mixture was stirred for 5 minutes. Boc-Glu(OSu)-OSu (0.0101 g, 0.0.229 mmol) was added and the reaction mixture was stirred under N_2 for 18 h. The reaction mixture was then concentrated to an oil under high vacuum. The oil was triturated with ethyl acetate. The product was filtered, washed with ethyl acetate, and dried under high vacuum to give 38.0 mg (55%) of the desired product. ESMS: Calcd. for $C_{68}H_{103}N_{19}O_{20}$, 1505.76; Found, 1504.9 [M-H]-1. Analytical HPLC, Method 1B, R_t = 19.797 min, Purity = 73%.

Part B. Preparation of Glu(cyclo{D-Tyr(3-aminopropyl)-Val-Arg-Gly-Asp})-cyclo{D-Tyr(3-aminopropyl)-Val-Arg-Gly-Asp}, SEQ ID NO: 9. TFA salt--

Please replace the paragraphs on page 134, l. 15 to page 135, l. 24 with the following rewritten paragraphs:

-- Boc-Glu(cyclo{D-Tyr(3-aminopropyl)-Val-Arg-Gly-Asp})-cyclo{D-Tyr(3-aminopropyl)-Val-Arg-Gly-Asp}, SEQ ID NO: 9, (0.035 g, 0.0232 mmol) was dissolved in methylene chloride (1 mL). Trifluoroacetic acid (1 mL) was added, and the reaction mixture was stirred for 2 h, concentrated to an oil under high vacuum and triturated with ether. The product obtained was filtered, washed with diethyl ether, and dried under high vacuum to give 30.7 mg (76%) of the desired product. ESMS: Calcd. for $C_{63}H_{95}N_{19}O_{18}$, 1405.71; Found, 1404.7 [M-H]-1. Analytical HPLC, Method 1B, R_t = 15.907 min, Purity = 77%.

Part C. Preparation of [2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-Glu(cyclo{D-Tyr(3-aminopropyl)-Val-Arg-Gly-Asp})-cyclo{D-Tyr(3-aminopropyl)-Val-Arg-Gly-Asp}, SEQ ID NO: 9.

To a solution of Glu(cyclo{D-Tyr(3-aminopropyl)-Val-Arg-Gly-Asp})-cyclo{D-Tyr(3-aminopropyl)-Val-Arg-Gly-Asp}, SEQ ID NO: 9, (0.025 g, 0.0143 mmol) in dimethylformamide (2 mL) was added triethylamine (6.0 μL, 0.0429 mmol) and the reaction mixture was stirred for 5 min. 2-[[[5-[[(2,5-Dioxo-1-pyrrolidinyl)oxy]carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid, monosodium salt (0.0076 g, 0.0172 mmol) was added, and the reaction mixture was stirred for 5 days, then concentrated to an oil under high vacuum. The oil was purified by Preparative HPLC Method 1 to give 12.0 mg (43%) of the desired product as a lyophilized solid. ESMS: Calcd. for $C_{76}H_{104}N_{22}O_{22}S$, 1708.7; Found, 1710.1 ($M+H^+$). Analytical HPLC, Method 1B, R_t = 17.218 min, Purity = 94%.

Example 4

Synthesis of cyclo(Arg-Gly-Asp-D-Tyr-Lys([2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])}, SEQ ID NO: 4--

Please replace the paragraphs on page 136, l. 3 to page 137, l. 1 with the following rewritten paragraphs:

--Part A. Preparation of cyclo{Arg(Tos)-Gly-Asp(OBzl)-D-Tyr(Bzl)-Lys(Cbz)}, SEQ ID NO: 4

The N-terminus Boc-protecting group of the peptide sequence Boc-Asp(OBzl)-D-Tyr(Bzl)-Lys(Z)-Arg(Tos)-Gly-oxime, SEQ ID NO: 30, resin was removed using standard deprotection (25% TFA in CH_2Cl_2). After eight washes with DCM, the resin was treated with 10% DIEA/DCM (2 x 10 min.). The resin was subsequently washed with DCM (x 5) and dried under high vacuum. The resin (1.8711 g, 0.44 mmol/g) was then suspended in DMF (15 mL). Glacial acetic acid (47.1 μL, 0.823 mmol) was added, and the reaction was heated at 60 °C for 72 h. The resin was filtered, and washed with DMF (2 x 10 mL). The filtrate was concentrated to an oil under high vacuum. The resulting oil was triturated with ethyl acetate. The solid thus obtained was filtered, washed with ethyl acetate, and dried under high vacuum to give 653.7 mg of the desired product. ESMS: Calcd. for $C_{56}H_{65}N_9O_{12}S$, 1087.45; Found, 1088.7 [M+H]+1. Analytical HPLC, Method 1A, R_t = 17.559 min, Purity = 82%.

Part B. Preparation of cyclo{Arg-Gly-Asp-D-Tyr-Lys}, SEQ ID NO: 4--

Please replace the paragraphs on page 137, l. 5 to page 138, l. 15 with the following rewritten paragraphs:

--Cyclo{Arg(Tos)-Gly-Asp(OBzl)-D-Tyr(Bzl)-Lys(Cbz)}, SEQ ID NO: 4, (0.200 g, 0.184 mmol) was dissolved in trifluoroacetic acid (0.6 mL) and cooled to -10 °C. Trifluoromethanesulfonic acid (0.5 mL) was added dropwise, maintaining the temperature at -10 °C. Anisole (0.1 mL) was added and the reaction mixture was stirred at -10 °C for 3 h. Diethyl ether was added, the reaction was cooled to -50 °C, and stirred for 1 h. The crude product was filtered, washed with diethyl ether, and dried under high vacuum. The crude product was purified by Preparative HPLC Method 1, to give 15.2 mg (10%) of the desired product as a lyophilized solid. HRMS: Calcd. for $C_{27}H_{41}N_9O_8$ +H, 620.3156; Found, 620.3145. Analytical HPLC, Method 1B, R_t = 8.179 min, Purity = 100%.

Part C. Preparation of cyclo{Arg-Gly-Asp-D-Tyr-Lys([2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])}, SEQ ID NO: 4

Cyclo{Arg-Gly-Asp-D-Tyr-Lys}, SEQ ID NO: 4, TFA salt (0.010 g, 0.0118 mmol) was dissolved in DMF (1 mL). Triethylamine (5.0 μL, 0.0354 mmol) was added, and after stirring for 5 min 2-[[[5-[[(2,5-Dioxo-1-pyrrolidinyl)oxy]carbonyl]-2-pyridinyl]hydrazono]-methyl]-benzenesulfonic acid, monosodium salt (0.0062 g, 0.0142 mmol) was added. The reaction mixture was stirred for 20 h and then concentrated to an oil under high vacuum. The oil was purified by Preparative HPLC Method 1 to give 6.2 mg (46%) of the desired product as a lyophilized solid. HRMS: Calcd. for $C_{40}H_{50}N_{12}O_{12}S$ + H, 923.3470; Found, 923.3486. Analytical HPLC, Method 1B, R_t = 11.954 min, Purity = 100%.

Example 5

Synthesis of cyclo{Arg-Gly-Asp-D-Phe-Lys([2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])}, SEQ ID NO: 3--

Please replace the paragraphs on page 138, l. 19 to page 139, l. 18 with the following rewritten paragraphs:

--Part A. Preparation of cyclo{Arg(Tos)-Gly-Asp(OBzl)-D-Phe-Lys(Cbz)}, SEQ ID NO: 3

The N-terminus Boc- protecting group of the peptide sequence Boc-Asp(OBzl)-D-Phe-Lys(Z)-Arg(Tos)-Gly-Oxime, SEQ ID NO: 31, resin was removed using standard deprotection (25% TFA in CH_2Cl_2). After eight washes with DCM, the resin was treated with 10% DIEA/DCM (2 x 10 min.). The resin was subsequently washed with DCM (x 5) and dried under high vacuum. The resin (1.7053 g, 0.44 mmol/g) was then suspended in dimethylformamide (15 mL). Glacial acetic acid (43.0 μL, 0.750 mmol) was added, and the reaction was heated to 60 °C for 72 h. The resin was filtered, and washed with DMF (2 x 10 mL). The filtrate was concentrated to an oil under high vacuum. The resulting oil was triturated with ethyl acetate. The solid thus obtained was filtered, washed with ethyl acetate, and dried under high vacuum to give 510.3 mg of the desired product. ESMS: Calcd. for $C_{49}H_{59}N_9O_{11}S$, 981.40; Found, 982.6 [M+H]+1. Analytical HPLC, Method 1A, R_t = 15.574 min, Purity = 89%.

Part B. Preparation of cyclo{Arg-Gly-Asp-D-Phe-Lys}, SEQ ID NO: 3--

Please replace the paragraphs on page 139, l. 22 to page 140, l. 32 with the following rewritten paragraphs:

--Cyclo{Arg(Tos)-Gly-Asp(OBzl)-D-Phe-Lys(Cbz)}, SEQ ID NO: 3, (0.200 g, 0.204 mmol) was dissolved in trifluoracetic acid (0.6 mL) and cooled to -10 °C. Trifluoromethanesulfonic acid (0.5 mL) was added dropwise, maintaining the temperature at -10 °C. Anisole (0.1 mL) was added and the reaction was stirred at -10 °C for 3 h. Diethyl ether was added, the reaction was cooled to -50 °C, and stirred for 1 h. The crude product was filtered, washed with diethyl ether, dried under high vacuum and purified by Preparative HPLC Method 1, to give 121.1 mg (71%) of the desired product as a lyophilized solid. HRMS: Calcd. for $C_{27}H_{41}N_9O_7$ +H, 604.3207; Found, 604.3206. Analytical HPLC, Method 1B, R_t = 11.197 min, Purity = 100%.

Part C. Preparation of cyclo{Arg-Gly-Asp-D-Phe-Lys([2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])}, SEQ ID NO: 3

Cyclo{Arg-Gly-Asp-D-Phe-Lys}, SEQ ID NO: 3, TFA salt (0.040 g, 0.0481 mmol) was dissolved in DMF (2 mL). Triethylamine (20.1 μL, 0.144 mmol) was added, and after 5 min of stirring 2-[[[5-[[(2,5-dioxo-1-pyrrolidinyl)oxy]carbonyl]-2-pyridinyl]hydrazono]-methyl]-benzenesulfonic acid, monosodium salt (0.0254 g, 0.0577 mmol) was added. The reaction mixture was stirred for 20 h and then concentrated to an oil under high vacuum. The oil was purified by Preparative HPLC Method 1 to give 38.2 mg (78%) of the desired product as a lyophilized solid. HRMS: Calcd. for $C_{40}H_{50}N_{12}O_{11}S$ + H, 907.3521; Found, 907.3534. Analytical HPLC, Method 1B, R_t = 14.122 min, Purity = 91%.

Example 6

Synthesis of [2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-Glu(cyclo{Lys-Arg-Gly-Asp-D-Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe}, SEQ ID NO: 8--

Please replace the paragraphs on page 142, l. 1 to page 142, l. 19 with the following rewritten paragraphs:

-- Part B. Preparation of Boc-Glu(cyclo{Lys-Arg-Gly-Asp-D-Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe}, SEQ ID NO: 8

To a solution of cyclo(Lys-Arg-Gly-Asp-D-Phe), SEQ ID NO: 17, (0.050 g, 0.0601 mmol) in dimethylformamide (2 mL) was added triethylamine (25.1 μL, 0.183 mmol). After stirring for 5 minutes Boc-Glu(OSu)-OSu (0.0133 g, 0.0301 mmol) was added. The reaction mixture was stirred under N_2 for 20 h, then concentrated to an oil under high vacuum and triturated with ethyl acetate. The product thus obtained was filtered, washed with ethyl acetate, and dried under high vacuum to give 43.7 mg (44%) of the desired product. ESMS: Calcd. for $C_{64}H_{95}N_{19}O_{18}$, 1417.71; Found, 1418.8 [M+H]+1. Analytical HPLC, Method 1B, R_t = 19.524 min, Purity = 73%.

Part C. Preparation of Glu(cyclo{Lys-Arg-Gly-Asp-D-Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe}, SEQ ID NO: 8, TFA salt.--

Please replace the paragraphs on page 142, l. 24 to page 143, l. 29 with the following rewritten paragraphs:

-- To a solution of Boc-Glu(cyclo{Lys-Arg-Gly-Asp-D-Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe}, SEQ ID NO: 8, (0.040 g, 0.0243 mmol) in methylene chloride (1 mL) was added trifluoroacetic acid (1 mL). The reaction mixture was stirred for 2 h, concentrated to an oil under high vacuum and

triturated with diethyl ether. The product was filtered, washed with diethyl ether, and dried under high vacuum to give 39.9 mg (100%) of the desired product. ESMS: Calcd. for $C_{59}H_{87}N_{19}O_{16}$, 1317.66; Found, 1318.9 [M+H]+1. Analytical HPLC, Method 1B, R_t = 15.410 min, Purity = 73%.

Part D. Preparation of [2-[[[5-[carbonyl]-2-pyridinyl]-hydrazono]methyl]-benzenesulfonic acid]-Glu(cyclo{Lys-Arg-Gly-Asp-D-Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe}, SEQ ID NO: 8

To a solution of Glu(cyclo{Lys-Arg-Gly-Asp-D-Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe}, SEQ ID NO: 8, (0.030 g, 0.0183 mmol) in dimethylformamide (3 mL) was added triethylamine (7.6 μL, 0.0549 mmol) and the reaction mixture was stirred for 5 min. 2-[[[5-[[(2,5-Dioxo-1-pyrrolidinyl)oxy]carbonyl]-2-pyridinyl]-hydrazono]methyl]-benzenesulfonic acid, monosodium salt (0.0096 g, 0.0220 mmol) was added, and the reaction mixture was stirred for 18 h, then concentrated to an oil under high vacuum. The oil was purified by Preparative HPLC Method 1 to give 11.0 mg (32%) of the desired product as a lyophilized solid. ESMS: Calcd. for $C_{72}H_{96}N_{22}O_{20}S$, 1620.7; Found, 1620.1 ($M-H^+$). Analytical HPLC, Method 1B, R_t = =16.753 min, Purity = 91%.

Example 7

Synthesis of [2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-Phe-Glu(cyclo{Lys-Arg-Gly-Asp-D-Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe}, SEQ ID NO: 5--

Please replace the paragraph on page 144, l. 3-4 with the following rewritten paragraph:

--Part A. Preparation of Phe-Glu(cyclo{Lys-Arg-Gly-Asp-D-Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe}, SEQ ID NO: 5--

Please replace the paragraphs on page 144, l. 8 to page 145, l. 25 with the following rewritten paragraphs:

--A solution of Glu(cyclo{Lys-Arg-Gly-Asp-D-Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe}, SEQ ID NO: 8, (23.4 mg, 0.014 mmol) and triethylamine (7.8 μL, 0.56 mmol) in DMF (2 mL) was stirred for 5 min. To this was added Boc-Phe-OSu (5.1 mg, 0.014 mmol) and the reaction mixture was stirred overnight at room temperature under nitrogen. DMF was removed in vacuo, and the resulting residue was dissolved in TFA (1.5 mL) and methylene chloride (1.5 mL). The solution was stirred for 2 h and concentrated in vacuo to provide 31 mg of the desired product as the TFA salt. ESMS: Calcd. for C68H96N20O17, 1464.7; Found, 1465.6 (M+H)+1. Analytical HPLC, Method 1B, Rt = =15.48 min, Purity = 95%.

Part B. Preparation of [2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-Phe-Glu(cyclo{Lys-Arg-Gly-Asp-D-Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe}, SEQ ID NO: 5

To a solution of Phe-Glu(cyclo{Lys-Arg-Gly-Asp-D-Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe}, SEQ ID NO: 5, (0.030 g, 0.016 mmol) in dimethylformamide (2 mL) was added triethylamine (9 μL, 0.064 mmol) and the reaction mixture was stirred for 5 min. 2-[[[5-[[(2,5-Dioxo-1-pyrrolidinyl)oxy]carbonyl]-2-pyridinyl]-hydrazono]methyl]-benzenesulfonic acid, monosodium salt (0.0099 g, 0.0220 mmol) was added, and the reaction mixture was stirred for 18 h, then concentrated under high vacuum. The residue was purified by preparative RP-HPLC Method 1 to give 7 mg (22%) of the desired product as a lyophilized solid (TFA salt). ESMS: Calcd. for C81H105N23O21S, 1767.8; Found, 1768.8 (M-H+). Analytical HPLC, Method 1B, Rt = = 17.68 min, Purity = 99%.

Example 8

Synthesis of cyclo{Arg-Gly-Asp-D-Nal-Lys([2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])}, SEQ ID NO: 6--

Please replace the paragraph on page 146, l. 1-2 with the following rewritten paragraph:

--Part A. Preparation of cyclo{Arg(Mtr)-Gly-Asp(OtBu)-D-Nal-Lys(Boc)}, SEQ ID NO: 6--

Please replace the paragraphs on page 146, l. 7-24 with the following rewritten paragraphs:

--The peptide Asp(OtBu)-D-Nal-Lys(Boc)-Arg(Mtr)-Gly, SEQ ID NO: 32, was obtained by automated solid phase peptide synthesis using Fmoc chemistry. A 100 mL round bottom flask was charged with HBTU (349 mg, 0.92 mmol) and DMF (10 mL). The solution was stirred at 60 °C for 5 min. To this a solution of Asp(OtBu)-D-Nal-Lys(Boc)Arg(Mtr)-Gly, SEQ ID NO: 32, (0.684 g) and Hunig's base (0.34 mL, 1.97 mmol.) in DMF (10 mL) was added and the solution stirred at 60 °C for 4 h under nitrogen. The solvent was then removed in vacuo and the residue was triturated with ethyl acetate. The solids were filtered and washed with ethyl acetate (3 x 5 mL) and dried in vacuo to give the desired product (520 mg, 86%). ESMS: Calcd. for $C_{50}H_{71}N_9O_{12}S$, 1021.5; Found, 1022.5 [M+H]+1. Analytical HPLC, Method 1A, R_t = 15.91 min (purity 99%).

Part B. Preparation of cyclo{Arg-Gly-Asp-D-Nal-Lys}, SEQ ID NO: 6, bis TFA salt--

Please replace the paragraphs on page 147, l. 3 to page 148, l. 7 with the following rewritten paragraphs:

--A solution of cyclo{Arg(Mtr)-Gly-Asp(OtBu)-D-Nal-Lys(Boc)}, SEQ ID NO: 6, (500 mg, 0.49 mmol), TFA (7 mL), triisopropylsilane (0.25 mL) and water (0.25 mL) was stirred at room temperature under nitrogen for 18 h. The solvents were removed in vacuo (over 3 h) and the residue triturated with diethyl ether to give the desired product as the TFA salt (426 mg, 98%). ESMS: Calcd. for $C_{31}H_{43}N_9O_7$, 653.3; Found, 654.3 [M+H]+1. Analytical HPLC, Method 1B, R_t = 13.30 min, Purity = 97%.

Part C. Preparation of cyclo{Arg-Gly-Asp-D-Nal-Lys([2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])}, SEQ ID NO: 6

Cyclo{Arg-Gly-Asp-D-Nal-Lys}, SEQ ID NO: 6, TFA salt (0.056 g, 0.064 mmol) was dissolved in DMF (2 mL). Triethylamine (27 μL, 0.19 mmol) was added, and after 5 min of stirring 2-[[[5-[[(2,5-dioxo-1-pyrrolidinyl)oxy]carbonyl]-2-pyridinyl]-hydrazono]-methyl]-benzenesulfonic acid, monosodium salt (0.039 g, 0.089 mmol) was added. The reaction mixture was stirred overnight, under nitrogen, and then concentrated to an oil under high vacuum. The oil was purified by Preparative HPLC Method 1 to give 49.3 mg (72%) of the desired product as a lyophilized solid (TFA salt). ESMS: Calcd. for $C_{44}H_{52}N_{12}O_{11}S$, 956.4; Found, 957.5 [M+H]+1. Analytical HPLC, Method 1B, R_t = 16.19 min, Purity = 99%.

Example 9

Synthesis of [2-[[[5-[carbonyl]-2-pyridinyl]-hydrazono]methyl]-benzenesulfonic acid]-Glu(cyclo{Lys-Arg-Gly-Asp-D-Nal})-cyclo{Lys-Arg-Gly-Asp-D-Nal}, SEQ ID NO: 7--

Please replace the paragraphs on page 148, l. 11 to page 149, l. 5 with the following rewritten paragraphs:

--Part A. Preparation of Boc-Glu(cyclo{Lys-Arg-Gly-Asp-D-Nal})-cyclo{Lys-Arg-Gly-Asp-D-Nal}, SEQ ID NO: 7

To a solution of cyclo{Lys-Arg-Gly-Asp-D-Nal}, SEQ ID NO: 18, (0.052 g, 0.059 mmol) in dimethylformamide (2 mL) was added triethylamine (25 μL). After stirring for 5 minutes Boc-Glu(OSu)-OSu (0.013 g, 0.029 mmol) was added. The reaction mixture was stirred under N_2 for 20 h, then concentrated to an oil under high vacuum and triturated with ethyl acetate. The product thus obtained was filtered, washed with ethyl acetate, and dried under high vacuum to give 35.2 mg of the desired product in crude form. ESMS: Calcd. for $C_{72}H_{99}N_{19}O_{18}$, 1517.7; Found, 760.1 [M+2H]+2. Analytical HPLC, Method 1B, R_t = 21.07 min (65%).

Part B. Preparation of Glu(cyclo{Lys-Arg-Gly-Asp-D-Nal})-cyclo{Lys-Arg-Gly-Asp-D-Nal}, SEQ ID NO: 7--

Please replace the paragraphs on page 149, l. 9 to page 150, l. 14 with the following rewritten paragraphs:

--To a solution of the crude Boc-Glu(cyclo{Lys-Arg-Gly-Asp-D-Nal})-cyclo{Lys-Arg-Gly-Asp-D-Nal}, SEQ ID NO: 7, (35.2 mg) in methylene chloride (1.5 mL) was added trifluoroacetic acid (1.5 mL). The reaction mixture was stirred for 2 h, concentrated to an oil under high vacuum and triturated with diethyl ether. The product was filtered, washed with diethyl ether, and dried under high vacuum to give 34.9 mg of the crude desired product (TFA salt). ESMS: Calcd. for $C_{67}H_{91}N_{19}O_{16}$, 1417.69; Found, 1418.7 [M+H]+1. Analytical HPLC, Method 1B, R_t = 19.1 min, Purity = 62%.

Part C. Preparation of [2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-Glu(cyclo{Lys-Arg-Gly-Asp-D-Nal})-cyclo{Lys-Arg-Gly-Asp-D-Nal}, SEQ ID NO: 7

To a solution of Glu(cyclo{Lys-Arg-Gly-Asp-D-Nal})-cyclo{Lys-Arg-Gly-Asp-D-Nal}, SEQ ID NO: 7, (34.9 mg) in dimethylformamide (2 mL) was added triethylamine (10 μL, 0.074 mmol) and the reaction mixture was stirred for 5 min. 2-[[[5-[[(2,5-Dioxo-1-pyrrolidinyl)oxy]carbonyl]-2-pyridinyl]-hydrazono]methyl]-benzenesulfonic acid, monosodium salt (15.2 mg, 0.0344 mmol) was added, and the reaction mixture was stirred for 18 h, then concentrated to an oil under high vacuum. The oil was purified by preparative RP-HPLC Method 1 to give 3 mg of the desired product (TFA salt). ESMS: Calcd. for $C_{80}H_{100}N_{22}O_{20}S$, 1720.7; Found, 1722.6 (M+H)+1. Analytical HPLC, Method 1B, R_t = =19.78 min, Purity = 92%.

Example 10

Synthesis of cyclo{Arg-Gly-Asp-Lys([2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])-D-Val}, SEQ ID NO: 10--

Please replace the paragraph on page 150, l. 18-19 with the following rewritten paragraph:

-- Part A. Preparation of cyclo{Arg(Tos)-Gly-Asp(OBzl)-Lys(Cbz)-D-Val}, SEQ ID NO: 10--

Please replace the paragraph on page 151, l. 30 with the following rewritten paragraph:

-- Part B. Preparation of cyclo{Arg-Gly-Asp-Lys-D-Val}, SEQ ID NO: 10--

Please replace the paragraphs on page 152, l. 3 to page 153, l. 13 with the following rewritten paragraphs:

--Cyclo{Arg(Tos)-Gly-Asp(OBzl)-Lys(Cbz)-D-Val}, SEQ ID NO: 10, (0.080 g, 0.0856 mmol) was dissolved in trifluoroacetic acid (0.6 mL) and cooled to -10 °C. Trifluoromethanesulfonic acid (0.5 mL) was added dropwise, maintaining the temperature at -10 °C. Anisole (0.1 mL) was added and the reaction mixture was stirred at -10 °C for 3 h. Diethyl ether was added, the reaction mixture cooled to -50 °C and stirred for 30 mins. The crude product obtained was filtered, washed with ether, dried under high vacuum and purified by Preparative HPLC Method 1, to give 44.2 mg (66%) of the desired product as a lyophilized solid. ESMS: Calcd. for $C_{23}H_{41}N_9O_7$, 555.31; Found, 556.3 [M+H]+1. Analytical HPLC, Method 1B, R_t = 8.959 min, Purity = 92%.

Part C. Preparation of cyclo{Arg-Gly-Asp-Lys([2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])-D-Val}, SEQ ID NO: 10

To a solution of cyclo{Arg-Gly-Asp-Lys-D-Val}, SEQ ID NO: 10, (0.036 g, 0.0459 mmol) in dimethylformamide (3 mL) was added triethylamine (19.2 μL, 0.0138 mmol) and stirred for 5 min. Methyl sulfoxide was added (0.7 mL) followed by 2-[[[5-[[(2,5-dioxo-1-pyrrolidinyl)oxy]carbonyl]-2-pyridinyl]-hydrazono]methyl]-benzenesulfonic acid, monosodium salt (0.0243 g, 0.0551 mmol) and the reaction mixture stirred for 20 h. The reaction mixture was concentrated to an oil under high vacuum and purified by Preparative HPLC Method 1 to give 13.9 mg (31%) of the desired product as a lyophilized solid. HRMS: Calcd. for $C_{36}H_{50}N_{12}O_{11}S$ +H, 859.3443; Found, 859.3503. Analytical HPLC, Method 1B, R_t = 13.479 min, Purity = 92%.

Example 11

Synthesis of [2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-Glu(cyclo{Lys-D-Val-Arg-Gly-Asp})-cyclo{Lys-D-Val-Arg-Gly-Asp}, SEQ ID NO: 20--

Please replace the paragraphs on page 153, l. 17 to page 154, l. 5 with the following rewritten paragraphs:

--Part A. Preparation of Boc-Glu(cyclo{Lys-D-Val-Arg-Gly-Asp})-cyclo{Lys-D-Val-Arg-Gly-Asp}, SEQ ID NO: 20

To a solution of cyclo{Lys-D-Val-Arg-Gly-Asp}, SEQ ID NO: 21, (0.400 g, 0.51 mmol) in dimethylformamide (7 mL) was added triethylamine (0.21 mL, 1.53 mmol). After stirring for 5 minutes Boc-Glu(OSu)-OSu (115 mg, 0.26 mmol) was added. The reaction mixture was stirred under N_2 for 20 h, then concentrated to an oil. The product thus obtained was partially purified by preparative RP-HPLC to give 124 mg of product. ESMS: Calcd. for $C_{56}H_{95}N_{19}O_{18}$, 1321.71; Found, 1322.6 [M+H]+1.

Part B. Preparation of Glu(cyclo{Lys-D-Val-Arg-Gly-Asp})-cyclo{Lys-D-Val-Arg-Gly-Asp}, SEQ ID NO: 21--

Please replace the paragraphs on page 154, l. 9 to page 155, l. 13 with the following rewritten paragraphs:

--To a solution of the impure Boc-Glu(cyclo{Lys-D-Val-Arg-Gly-Asp})-cyclo{Lys-D-Val-Arg-Gly-Asp}, SEQ ID NO: 21, (0.124 g) in methylene chloride (5 mL) was added trifluoroacetic acid (5 mL). The reaction mixture was stirred for 2 h, concentrated to an oil under high vacuum and triturated with diethyl ether. The product was filtered, washed with diethyl ether, and dried under high vacuum to give 16.2 mg of the desired product after

RP-HPLC (TFA salt). ESMS: Calcd. for $C_{51}H_{87}N_{19}O_{16}$, 1221.66; Found, 1222.6 [M+H]+1. Analytical HPLC, Method 1B, R_t = 11.43 min, Purity = 93%.

Part C. Preparation of [2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-Glu(cyclo{Lys-D-Val-Arg-Gly-Asp})-cyclo{Lys-D-Val-Arg-Gly-Asp}, SEQ ID NO: 21

To a solution of Glu(cyclo{Lys-D-Val-Arg-Gly-Asp})-cyclo{Lys-D-Val-Arg-Gly-Asp}, SEQ ID NO: 21, (0.016 g, 0.01 mmol) in dimethylformamide (2 mL) was added triethylamine (4.2 μL) and the reaction mixture was stirred for 5 min. 2-[[[5-[[(2,5-Dioxo-1-pyrrolidinyl)oxy]carbonyl]-2-pyridinyl]-hydrazono]methyl]-benzenesulfonic acid, monosodium salt (0.0063 g, 0.014 mmol) was added, and the reaction mixture was stirred for 18 h, then concentrated to an oil under high vacuum. The residue was purified by preparative RP-HPLC Method 1 to give the desired product (TFA salt). ESMS: Calcd. for $C_{64}H_{96}N_{22}O_{20}S$, 1524.7; Found, 1525.7 (M+H)+1. Analytical HPLC, Method 1B, R_t = =13.20 min, Purity = 99%.

Example 12

Synthesis of {cyclo(Arg-D-Val-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-D-Asp-Gly}, SEQ ID NO: 2--

Please replace the paragraphs on page 155, l. 18 to page 156, l. 14 with the following rewritten paragraphs:

-- Part A: Preparation of cyclo{Arg(Tos)-D-Val-D-Tyr(N-Cbz-3-aminopropyl)-D-Asp(OBzl)-Gly}, SEQ ID NO: 2

The N-terminus Boc-protecting group of the peptide sequence Boc-Arg(Tos)-D-Val-D-Tyr(N-Cbz-aminopropyl)-D-Asp(OBzl)-Gly-Oxime, SEQ ID NO: 2, resin was removed using standard deprotection (50% TFA in CH_2Cl_2). After washing with DCM (8x), the resin was neutralized with 10% DIEA/DCM (2 x 10 min). The resin was washed with DCM (5x) and dried under high vacuum overnight. The resin (1.08 g, 0.36 mmol/g) was then suspended in N,N-dimethylformamide (12 mL). Glacial acetic acid (67 mL, 1.16 mmol) was added and the reaction mixture was heated to 55 ^{o}C for 72 h. The resin was filtered and washed with DMF (3 x 10 mL). The filtrate was concentrated under high vacuum to give an oil. The resulting oil was triturated with ethyl acetate. The solid obtained was purified by reverse-phase HPLC (Vydac C18 column, 18 to 90% acetonitrile gradient containing 0.1% TFA, R_t=15.243 min) to afford 101 mg of a white powdered product (30%). ESMS: Calculated for $C_{44}H_{57}N_9O_{12}S$, 935.3847 Found 936.5 [M+H]+1.

Part B: Preparation of cyclo{Arg-D-Val-D-Tyr(3-aminopropyl)-D-Asp-Gly}, SEQ ID NO: 2--

Please replace the paragraphs on page 156, l. 18 to page 157, l. 30 with the following rewritten paragraphs:

--The protected cyclic peptide cyclo{Arg(Tos)-D-Val-D-Tyr(N-Cbz-3-aminopropyl)-D-Asp(OBzl)-Gly}, SEQ ID NO: 2, (90 mg, 0.0961 mmol) was dissolved in trifluoroacetic acid (0.95 mL) and cooled to -10 ^{o}C in a dry ice/acetone bath. To this solution was added trifluoromethanesulfonic acid (0.1.16 mmol), followed by anisole (190 mL). The reaction mixture was stirred at -16 ^{o}C for 3 h. The dry ice/acetone bath was then cooled to -35 ^{o}C and cold ether (40 mL) was added to the solution. The mixture was stirred for 30 min at -35 ^{o}C, then

cooled to -50 °C and stirred for another 30 min. The crude product was filtered, redissolved in water/acetonitrile (1/1), lyophilized, and purified by reverse-phase HPLC (Vydac C18 Column, 1.8 to 90% acetonitrile gradient containing 0.1% TFA, R_t=13.383 min) to generate 17 mg of the title product (27%). ESMS: Calculated for $C_{29}H_{45}N_9O_8$, 647.3391 Found 648.2 [M+H]+1.

Part C: Preparation of {cyclo(Arg-D-Val-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-D-Asp-Gly}, SEQ ID NO: 2

A solution of cyclo{Arg-D-Val-D-Tyr(3-aminopropyl)-D-Asp-Gly}, SEQ ID NO: 2, (14 mg, 0.0216 mmol) in N,N-dimethylformamide (2 mL) was added triethylamine (15 mL, 0.108 mmol) and stirred at room temperature for 10 min. 2-[[[5-[[(2,5-Dioxo-1-pyrrolidinyl)oxy]carbonyl-2-pyridinyl]-hydrazono]methyl-benzenesulfonic acid, monosodium salt (11 mg, 0.0260 mmol) was added, and the mixture was stirred for 18 h. The mixture was concentrated under high vacumm and the residue was purified by reverse-phase HPLC (Vydac C18 Column, 1.8 to 90% acetonitrile gradient containing 0.1% TFA, R_t=16.264 min) to afford 10 mg of a white powdered product (49%). ESMS: Calculated for $C_{42}H_{54}N_{12}O_{12}S$, 950.3705 Found 951.3 [M+H]+1.

Example 13

Synthesis of cyclo{D-Lys([2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])-D-Phe-D-Asp-Gly-Arg}, SEQ ID NO: 11--

Please replace the paragraphs on page 158, l. 3-26 with the following rewritten paragraphs:

--Part A: Preparation of cyclo{D-Lys(Cbz)-D-Phe-D-Asp(OBzl)-Gly-Arg(Tos)}, SEQ ID NO: 11

The N-terminus Boc- protecting group of the peptide sequence Boc-Arg(Tos)-D-Lys(Cbz)-D-Phe-D-Asp(OBzl)-Gly-Oxime, SEQ ID NO: 22, resin was removed using standard deprotection (25% TFA in CH_2Cl_2). After eight washes with DCM, the resin was treated with 10% DIEA/DCM (2 x 10 min.). The resin was subsequently washed with DCM (x 5) and dried under high vacuum. The resin (1.93 g, 0.44 mmol/g) was then suspended in dimethylformamide (15 mL). Glacial acetic acid (77 μL) was added, and the reaction was heated to 60 °C for 72 h. The resin was filtered, and washed with DMF (2 x 10 mL). The filtrate was concentrated to an oil under high vacuum. The resulting oil was triturated with ethyl acetate. The solid thus obtained was filtered, washed with ethyl acetate, and dried under high vacuum to give the desired product which was then purified by preparative RP-HPLC (yield = 252 mg). ESMS: Calcd. for $C_{49}H_{59}N_9O_{11}S$, 981.40; Found, 982.3 [M+H]+1. Analytical HPLC, Method 1A, R_t = 14.577 min.

Part B: Preparation of cyclo{D-Lys-D-Phe-D-Asp-Gly-Arg}, SEQ ID NO: 11, TFA salt--

Please replace the paragraphs on page 159, l. 3 to page 160, l. 12 with the following rewritten paragraphs:

--Cyclo{D-Lys(Cbz)-D-Phe-D-Asp(OBzl)-Gly-Arg(Tos)}, SEQ ID NO: 11, (0.152 g, 0.155 mmol) was dissolved in trifluoracetic acid (1.55 mL) and cooled to -16 °C. Trifluoromethanesulfonic acid (1.86 mL) was added dropwise, maintaining the temperature

at -16 °C. Anisole (0.31 mL) was added and the reaction was stirred at -16 °C for 3 h. Diethyl ether was added, the reaction was cooled to -35 °C, and stirred for 20 min. The crude product was filtered, washed with diethyl ether, dried under high vacuum and purified by Preparative HPLC Method 1 , to give 69 mg (~53%) of the desired product as a lyophilized solid (TFA salt). ESMS: Calcd. for $C_{27}H_{41}N_9O_7$ +H, 604.3207; Found, 604.4. Analytical HPLC, Method 1B, R_t = 10.35 min, Purity = 93%.

Part C: Preparation of cyclo{D-Lys([2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])-D-Phe-D-Asp-Gly-Arg}, SEQ ID NO: 11, TFA salt

Cyclo{D-Lys-D-Phe-D-Asp-Gly-Arg}, SEQ ID NO: 11, TFA salt (0.056 g, 0.0673 mmol) was dissolved in DMF (2 mL). Triethylamine (28 μL, 0.202 mmol) was added, and after 5 min of stirring 2-[[[5-[[(2,5-dioxo-1-pyrrolidinyl)oxy]carbonyl]-2-pyridinyl]hydrazono]-methyl]-benzenesulfonic acid, monosodium salt (0.029 g, 0.0673 mmol) was added. The reaction mixture was stirred for 70 h and then concentrated to an oil under high vacuum. The oil was purified by preparative HPLC Method 1 to give 14 mg (78%) of the desired product as a lyophilized solid (TFA salt). ESMS: Calcd. for $C_{40}H_{50}N_{12}O_{11}S$ + H, 907.3521; Found, 907.3. Analytical HPLC, Method 1B, R_t = 14.17 min, Purity = 99%.

Example 14

Synthesis of [2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-Glu(cyclo{D-Lys-D-Phe-D-Asp-Gly-Arg})-cyclo{D-Lys-D-Phe-D-Asp-Gly-Arg}, SEQ ID NO: 12--

Please replace the paragraphs on page 160, l. 16 to page 161, l. 11 with the following rewritten paragraphs:

-- Part A. Preparation of Boc-Glu(cyclo{D-Lys-D-Phe-D-Asp-Gly-Arg})-cyclo{D-Lys-D-Phe-D-Asp-Gly-Arg}, SEQ ID NO: 12

To a solution of cyclo(D-Lys-D-Phe-D-Asp-Gly-Arg), SEQ ID NO: 11, (0.190 g, 0.228 mmol) in dimethylformamide (5 mL) was added triethylamine (95 μL, 0.684 mmol). After stirring for 5 minutes Boc-Glu(OSu)-OSu (0.050 g, 0.114 mmol) was added. The reaction mixture was stirred under N_2 for 20 h, then concentrated to an oil under high vacuum and triturated with ethyl acetate. The product thus obtained was filtered, washed with ethyl acetate, and dried under high vacuum to give 172 mg of the desired product in crude form. ESMS: Calcd. for $C_{64}H_{95}N_{19}O_{18}$, 1417.71; Found, 1418.7 [M+H]+1. Analytical HPLC, Method 1B, R_t = 16.8 min.

Part B. Preparation of Glu(cyclo{D-Lys-D-Phe-D-Asp-Gly-Arg})-cyclo{D-Lys-D-Phe-D-Asp-Gly-Arg}, SEQ ID NO: 12--

Please replace the paragraphs on page 161, l. 15 to page 162, l. 7 with the following rewritten paragraphs:

-- To a solution of the crude Boc-Glu(cyclo{D-Lys-D-Phe-D-Asp-Gly-Arg})-cyclo{D-Lys-D-Phe-D-Asp-Gly-Arg}, SEQ ID NO: 12, (0.172 g) in methylene chloride (4.5 mL) was added trifluoroacetic acid (4.5 mL). The reaction mixture was stirred for 2 h, concentrated to an oil under high vacuum and triturated with diethyl ether. The product was filtered, washed with diethyl ether, and dried under high vacuum to give 38 mg of the desired product after RP-HPLC as a lyophilized solid (TFA salt). ESMS: Calcd. for $C_{59}H_{87}N_{19}O_{16}$, 1317.66;

Found, 1318.9 [M+H]+1. Analytical HPLC, Method 1B, R_t = 13.06 min, Purity = 93%.

Part C. Preparation of [2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-Glu(cyclo{D-Lys-D-Phe-D-Asp-Gly-Arg})-cyclo{D-Lys-D-Phe-D-Asp-Gly-Arg}, SEQ ID NO: 12--

Please replace the paragraphs on page 162, l. 11 to page 163, l. 7 with the following rewritten paragraphs:

--To a solution of Glu(cyclo{D-Lys-D-Phe-D-Asp-Gly-Arg})-cyclo{D-Lys-D-Phe-D-Asp-Gly-Arg}, SEQ ID NO: 12, (0.025 g, 0.015 mmol) in dimethylformamide (2 mL) was added triethylamine (6.3 μL, 0.045 mmol) and the reaction mixture was stirred for 5 min. 2-[[[5-[[(2,5-Dioxo-1-pyrrolidinyl)oxy]carbonyl]-2-pyridinyl]-hydrazono]methyl]-benzenesulfonic acid, monosodium salt (0.0092 g, 0.0210 mmol) was added, and the reaction mixture was stirred for 18 h, then concentrated to an oil under high vacuum. The oil was purified by Preparative HPLC Method 1 to give 12.5 mg of the desired product as a lyophilized solid (TFA salt). ESMS: Calcd. for $C_{72}H_{96}N_{22}O_{20}S$, 1620.7; Found, 1622.5 (M+H)+1. Analytical HPLC, Method 1B, R_t = =14.62 min, Purity = 96%.

Example 15

Synthesis of cyclo{D-Phe-D-Lys([2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])-D-Asp-Gly-Arg}, SEQ ID NO: 13--

Please replace the paragraphs on page 163, l. 11 to page 164, l. 7 with the following rewritten paragraphs:

--Part A. Preparation of cyclo{D-Phe-D-Lys(Cbz)-D-Asp(OBzl)-Gly-Arg(Tos)}, SEQ ID NO: 13

The N-terminus Boc- protecting group of the peptide sequence Boc-Arg(Tos)-D-Phe-D-Lys(Cbz)-D-Asp(OBzl)-Gly-Oxime, SEQ ID NO: 23, resin was removed using standard deprotection (25% TFA in CH_2Cl_2). After eight washes with DCM, the resin was treated with 10% DIEA/DCM (2 x 10 min.). The resin was subsequently washed with DCM (x 5) and dried under high vacuum. The resin (1.5 g, 0.44 mmol/g) was then suspended in dimethylformamide (12 mL). Glacial acetic acid (61 μL) was added, and the reaction was heated to 60 °C for 72 h. The resin was filtered, and washed with DMF (2 x 10 mL). The filtrate was concentrated to an oil under high vacuum. The resulting oil was triturated with ethyl acetate. The solid thus obtained was filtered, washed with ethyl acetate, and dried under high vacuum to give the desired product (yield = 370 mg). ESMS: Calcd. for $C_{49}H_{59}N_9O_{11}S$, 981.40; Found, 982.4 [M+H]+1. Analytical HPLC, Method 1A, R_t = 14.32 min (purity 60%).

Part B. Preparation of cyclo{D-Phe-D-Lys-D-Asp-Gly-Arg}, SEQ ID NO: 13, bis TFA Salt--

Please replace the paragraphs on page 164, l. 10 to page 165, l. 18 with the following rewritten paragraphs:

--The crude cyclo{D-Phe-D-Lys(Cbz)-D-Asp(OBzl)-Gly-Arg(Tos)}, SEQ ID NO: 13, (0.146 g) was dissolved in trifluoracetic acid (1.5 mL) and cooled to -16 °C. Trifluoromethanesulfonic acid (1.8 mL) was added dropwise, maintaining the temperature at -

16 °C. Anisole (0.3 mL) was added and the reaction was stirred at -16 °C for 3 h. Diethyl ether was added, the reaction was cooled to -35 °C, and stirred for 20 min. The crude product was filtered, washed with diethyl ether, dried under high vacuum and purified by Preparative HPLC Method 1, to give 100 mg of the desired product as a lyophilized solid (TFA salt). ESMS: Calcd. for $C_{27}H_{41}N_9O_7$ +H, 604.3; Found, 604.3. Analytical HPLC, Method 1B, R_t = 10.25 min, Purity = 90%.

Part C. Preparation of cyclo{D-Phe-D-Lys([2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])-D-Asp-Gly-Arg}, SEQ ID NO: 13

Cyclo{D-Phe-D-Lys-D-Asp-Gly-Arg}, SEQ ID NO: 13, TFA salt (0.090 g, 0.108 mmol) was dissolved in DMF (2 mL). Triethylamine (45 μL, 0.324 mmol) was added, and after 5 min of stirring 2-[[[5-[[(2,5-dioxo-1-pyrrolidinyl)oxy]carbonyl]-2-pyridinyl]hydrazono]-methyl]-benzenesulfonic acid, monosodium salt (0.048 g, 0.108 mmol) was added. The reaction mixture was stirred for 70 h and then concentrated to an oil under high vacuum. The oil was purified by Preparative HPLC Method 1 to give 10 mg of the desired product as a lyophilized solid (TFA salt). ESMS: Calcd. for $C_{40}H_{50}N_{12}O_{11}S$ + H, 907.4; Found, 907.3. Analytical HPLC, Method 1B, R_t = 13.47 min, Purity = 89%.

Example 16

Synthesis of cyclo{N-Me-Arg-Gly-Asp-ATA-D-Lys, SEQ ID NO: 14, ([2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])}--

Please replace the paragraphs on page 165, l. 21 to page 166, l. 16 with the following rewritten paragraphs:

--Part A: Preparation of cyclo{N-Me-Arg(Tos)-Gly-Asp(OBzl)-ATA-D-Lys(Cbz)}, SEQ ID NO: 14

The N-terminus Boc-protecting group of the peptide sequence Boc-Asp(OBzl)-ATA-D-Lys(Z)-N-Me-Arg(Tos)-Gly-Oxime, SEQ ID NO: 24, resin was removed using standard deprotection (50% TFA in CH_2Cl_2). After washing with DCM (8x), the resin was treated with 10% DIEA/DCM (2 x 10 min). The resin was washed with DCM (5x) and dried under high vacuum overnight. The resin (1.24 g, 0.39 mmol/g) was then suspended in DMF (12 mL). Glacial acetic acid (67 mL, 1.16 mmol) was added and the reaction mixture was heated at 50 °C for 72 h. The resin was filtered and washed with DMF (3 x 10 mL). The filtrate was concentrated under high vacuum to give an oil. The resulting oil was triturated with ethyl acetate. The solid obtained was purified by reverse-phase HPLC (Vydac C18 column, 18 to 90% acetonitrile gradient containing 0.1% TFA, R_t=14.129 min) to afford 42 mg (9%) of the desired product as a lyophilized solid. ESMS: Calculated for $C_{46}H_{56}N_{10}O_{11}S_2$, 988.3571 Found 989.4 [M+H]+1.

Part B: Preparation of cyclo{N-Me-Arg-Gly-Asp-ATA-D-Lys}, SEQ ID NO: 14--

Please replace the paragraphs on page 166, l. 20 to page 167, l. 29 with the following rewritten paragraphs:

--Cyclo{N-Me-Arg(Tos)-Gly-Asp(OBzl)-ATA-D-Lys(Cbz)}, SEQ ID NO: 14, (36 mg, 0.0364 mmol) was dissolved in trifluoroacetic acid (0.364 mL) and cooled to -10 °C in a dry ice/acetone bath. To this solution was added trifluoromethanesulfonic acid

(0.437 mmol), followed by anisole (70 mL). The reaction mixture was stirred at -10 °C for 3 h. The dry ice/acetone bath was then cooled to -35 °C and cold ether (40 mL) was added to the solution. The mixture was stirred for 30 min at -35 °C, then cooled further to -50 °C and stirred for another 30 min. The crude product was filtered, redissolved in water/acetonitrile (1/1), and lyophilized to generate 35 mg of the title product (100%). ESMS: Calculated for $C_{24}H_{38}N_{10}O_7S$, 610.2646 Found 611.4 [M+H]+1.

Part C: Preparation of cyclo{N-Me-Arg-Gly-Asp-ATA-D-Lys([2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])}, SEQ ID NO: 14

To a solution of cyclo{N-Me-Arg-Gly-Asp-ATA-D-Lys}, SEQ ID NO: 14, (31 mg, 0.051 mmol) in DMF (2 mL) was added triethylamine (28 mL, 0.204 mmol) and the reaction mixture stirred at room temperature for 10 min. 2-[[[5-[[(2,5-Dioxo-1-pyrrolidinyl)-oxy]carbonyl-2-pyridinyl]hydrazono]methyl-benzenesulfonic acid, monosodium salt (27 mg, 0.0612 mmol) was added, the mixture stirred for 18 h and then concentrated under high vacumm. The residue obtained was purified by reverse-phase HPLC (Shandon HS-BDS column, 3 to 10% acetonitrile, R_t=13.735 min) to afford 4 mg (8.8%) of the desired product as a lyophilized solid. ESMS: Calculated for $C_{37}H_{47}N_{13}O_{11}S_2$, 913.2959 Found 914.5 [M+H]+1.

Example 17

Synthesis of cyclo{Cit-Gly-Asp-D-Phe-Lys([2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])}, SEQ ID NO: 15--

Please replace the paragraphs on page 168, l. 3-25 with the following rewritten paragraphs:

--Part A. Preparation of cyclo{Cit-Gly-Asp(OtBu)-D-Phe-Lys(Boc)}, SEQ ID NO: 15

The peptide Asp(OtBu)-D-Phe-Lys(Boc)-Cit-Gly, SEQ ID NO: 25, was obtained by automated solid phase peptide synthesis using Fmoc chemistry (see general procedure). A 100 mL round bottom flask was charged with HBTU (271 mg, 0.71 mmol) and DMF (10 mL). The solution was stirred at 60 °C for 5 min. To this a solution of Asp(OtBu)-D-Phe-Lys(Boc)-Cit-Gly, SEQ ID NO: 25, (0.456 g) and Hunig's base (0.27 mL, 1.53 mmol.) in DMF (10 mL) was added and the solution stirred at 60 °C for 4 h under nitrogen. The solvent was then removed in vacuo and the residue was triturated with ethyl acetate. The solids were filtered and washed with ethyl acetate (3 x 6 mL) and dried in vacuo to give the desired product (305 mg, 78%). ESMS: Calcd. for $C_{36}H_{56}N_8O_{10}$, 760.4; Found, 761.4 [M+H]+1. Analytical HPLC, Method 1A, R_t = 11.8 min (purity 99%).

Part B. Preparation of cyclo{Cit-Gly-Asp(OtBu)-D-Phe-Lys(Boc)}, SEQ ID NO: 15--

Please replace the paragraphs on page 169, l. 3 to page 170, l. 2 with the following rewritten paragraphs:

-- A solution of cyclo{Cit-Gly-Asp(OtBu)-D-Phe-Lys(Boc)}, SEQ ID NO: 15, (287 mg, 0.38 mmol), TFA (6 mL), triisopropylsilane (0.25 mL) and water (0.25 mL) was stirred at room temperature under nitrogen for 4 h. The solvents were removed in vacuo (over 3 h) and the residue triturated with diethyl ether, filtered and washed with ether to give the desired product (315 mg) (TFA salt). ESMS: Calcd. for

C27H40N8O8, 604.3; Found, 605.4 [M+H]+1. Analytical HPLC, Method 1B, Rt = 9.6 min, Purity = 97%.

Part C. Preparation of cyclo{Cit-Gly-Asp-D-Phe-Lys([2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])}, SEQ ID NO: 15

Cyclo{Cit-Gly-Asp-D-Phe-Lys}, SEQ ID NO: 15, TFA salt (0.044 g) was dissolved in DMF (2 mL). Triethylamine (22 μL, 0.156 mmol) was added, and after 5 min of stirring 2-[[[5-[[(2,5-dioxo-1-pyrrolidinyl)oxy]carbonyl]-2-pyridinyl]hydrazono]-methyl]-benzenesulfonic acid, monosodium salt (0.032 g, 0.073 mmol) was added. The reaction mixture was stirred overnight, under nitrogen, and then concentrated under high vacuum. The residue was purified by preparative RP-HPLC Method 1 to give 37 mg (70%) of the desired product as a lyophilized solid (TFA salt). ESMS: Calcd. for C40H49N11O12S, 907.3; Found, 908.4 [M+H]+1. Analytical HPLC, Method 1B, Rt = 14.15 min, Purity = 99%.--

Please replace the paragraph on page 171, l. 10-12 with the following rewritten paragraph:

--Synthesis of 2-(1,4,7,10-tetraaza-4,7,10-tris(carboxymethyl)-1-cyclododecyl)acetyl-Glu(cyclo{Lys-Arg-Gly-Asp-D-Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe}, SEQ ID NO: 8--

Please replace the paragraph on page 171, l. 16-19 with the following rewritten paragraph:

--Synthesis of 2-(1,4,7,10-tetraaza-4,7,10-tris(carboxymethyl)-1-cyclododecyl)acetyl-Glu(cyclo{Lys-Arg-Gly-Asp-D-Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe}, SEQ ID NO: 8--

Please replace the paragraphs on page 172, l. 3 to page 173, l. 9 with the following rewritten paragraphs:

--To a solution of tris(t-butyl)-1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid (28 mg, 0.049 mmol) and Hunig's base (14 μL) in DMF (2 mL) was added HBTU (17 mg, 0.0456 mmol) and the mixture stirred for 5 min. To this was added a solution of Glu(cyclo{Lys-Arg-Gly-Asp-D-Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe}, SEQ ID NO: 8, (54.1 mg, 0.0326 mmol) in DMF (1 mL) and the reaction mixture allowed to stir under nitrogen at room temperature for 4 h. The solvent was removed in vacuo and the residue purified by preparative RP-HPLC to give the product as a lyophilized solid (18.3 mg) (TFA salt). ESMS: Calcd. for $C_{87}H_{137}N_{23}O_{23}$, 1872.0; Found, 937.2 [M+2H]+2. Analytical HPLC, Method 1B, R_t = 19.98 min, Purity = 99%.

Part B. Preparation of 2-(1,4,7,10-tetraaza-4,7,10-tris(carboxymethyl)-1-cyclododecyl)acetyl-Glu(cyclo{Lys-Arg-Gly-Asp-D-Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe}, SEQ ID NO: 8

A solution of 2-(1,4,7,10-tetraaza-4,7,10-tris(t-butoxycarbonylmethyl)-1-cyclododecyl)acetyl-Glu(cyclo{Lys-Arg-Gly-Asp-D-Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe}, SEQ ID NO: 8, (18.3 mg, 8.71 mmol) in TFA (3 mL) was stirred at room temperature under nitrogen for 5 h. The solution was concentrated in vacuo and the residue was purified by preparative RP-HPLC to give 8 mg (45%) of the desired product as the lyophilized solid (TFA salt). ESMS: Calcd. for $C_{75}H_{113}N_{23}O_{23}$, 1703.8; Found, 853.0 [M+2H]+2. Analytical HPLC, Method 1B, R_t = 13.13 min, Purity = 99%.

Example 19

Synthesis of cyclo{Arg-Gly-Asp-D-Phe-Lys(DTPA)}, SEQ ID NO: 3--

Please replace the paragraphs on page 173, l. 13-27 with the following rewritten paragraphs:

-- To a solution of cyclo{Arg-Gly-Asp-D-Phe-Lys}, SEQ ID NO: 3, (0.050 g, 0.0601 mmol) in DMF (2 mL) was added triethylamine (41.9 μL, 0.301 mmol). This solution was added dropwise over 4 h to a solution of diethylenetriaminepentaacetic dianhydride (0.1074 g, 0.301 mmol) in DMF (2 mL) and methyl sulfoxide (2 mL). The reaction mixture was then stirred for 16 h, concentrated to an oil under high vacuum and purified by Preparative HPLC Method 1 to give 29.9 mg (46%) of the desired product as a lyophilized solid. ESMS: Calcd. for $C_{41}H_{62}N_{12}O_{16}$, 978.4; Found, 977.5 ($M-H^+$). Analytical HPLC, Method 1B, R_t = 11.916 min. Purity = 100%.

Example 20

Synthesis of cyclo{Arg-Gly-Asp-D-Phe-Lys}$_2$(DTPA), SEQ ID NO: 3--

Please replace the paragraph on page 174, l. 10-11 with the following rewritten paragraph:

--Synthesis of Cyclo{Arg-Gly-Asp-D-Tyr(N-DTPA-3-aminopropyl)-Val}, SEQ ID NO: 1--

Please replace the paragraphs on page 174, l. 16 to page 175, l. 13 with the following rewritten paragraphs:

-- To a solution of cyclo{Arg-Gly-Asp-D-Tyr(3-aminopropyl)-Val}, SEQ ID NO: 1, (0.050 g, 0.0571 mmol) in dimethylformamide (2 mL) was added triethylamine (39.8 μL, 0.286 mmol). This solution was added dropwise over 5 h to a solution of diethylenetriamine-pentaacetic dianhydride (0.1020

g, 0.286 mmol) in methyl sulfoxide (2 mL). The reaction mixture was stirred for an additional 18 h, then concentrated to an oil under high vacuum and purified by Preparative HPLC Method 1 to give 41.9 mg (65%) of the desired product as a lyophilized solid. ESMS: Calcd. for $C_{43}H_{66}N_{12}O_{17}$, 1022.5; Found, 1021.4 ($M-H^+$). Analytical HPLC, Method 1B, R_t = 15.690 min, Purity = 96%.

Example 22

Synthesis of cyclo{Orn(d-N-2-Imidazolinyl)-Gly-Asp-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-Val}, SEQ ID NO: 33--

Please replace the paragraphs on page 175, l. 17 to page 177, l. 16 with the following rewritten paragraphs:

-- Part A: Preparation of cyclo{Orn(d-N-1-Tos-2-Imidazolinyl)-Gly-Asp(OBzl)-D-Tyr(N-Cbz-3-aminopropyl)-Val}, SEQ ID NO: 33

The N-terminus Boc- protecting group of the peptide sequence Boc-Asp(OBzl)-D-Tyr(N-Cbz-aminopropyl)-Val-Orn(d-N-1-Tos-2-Imidazolinyl)-Gly-Oxime, SEQ ID NO: 34, resin is removed using standard deprotection (25% TFA in CH_2Cl_2). After eight washes with DCM, the resin is treated with 10% DIEA/DCM (2 x 10 min.). The resin is subsequently washed with DCM (x 5) and dried under high vacuum. The resin (1.75 g, 0.55 mmol/g) is then suspended in dimethylformamide (15 mL). Glacial acetic acid (55.0 μL, 0.961 mmol) is added, and the reaction mixture is heated at 50 °C for 72 h. The resin is filtered, and washed with DMF (2 x 10 mL). The filtrate is concentrated to an oil under high vacuum. The resulting oil is triturated with ethyl acetate. The solid is filtered, washed with ethyl acetate, and is dried under high vacuum to obtain the desired product.

Part B: Preparation of cyclo{Orn(d-N-2-Imidazolinyl)-Gly-Asp-D-Tyr(3-aminopropyl)-Val}, SEQ ID NO: 33, Trifluoroacetic acid salt.

Cyclo{Orn(d-N-1-Tos-2-Imidazolinyl)-Gly-Asp(OBzl)-D-Tyr(N-Cbz-3-aminopropyl)-Val}, SEQ ID NO: 33, (0.146 mmol) is dissolved in trifluoroacetic acid (0.6 mL) and cooled to -10 °C. Trifluoromethanesulfonic acid (0.5 mL) is added dropwise, maintaining the temperature at -10 °C. Anisole (0.1 mL) is added and the reaction mixture is stirred at -10 °C for 3 h. Diethyl ether is added, the reaction mixture cooled to -35 °C and then stirred for 30 min. The reaction mixture is cooled further to -50 °C and stirred for 30 min. The crude product is filtered, washed with diethyl ether, dried under high vacuum, and is purified by preparative HPLC to obtain the desired product.

Part C. Preparation of cyclo{Orn(d-N-2-Imidazolinyl)-Gly-Asp-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-Val}, SEQ ID NO: 33

Cyclo{Orn(d-N-2-Imidazolinyl)-Gly-Asp-D-Tyr(3-aminopropyl)-Val}, SEQ ID NO: 33, trifluoroacetic acid salt (0.0228 mmol) is dissolved in DMF (1 mL). Triethylamine (0.0648 mmol) is added, and after 5 min of stirring 2-[[[5-[[(2,5-dioxo-1-pyrrolidinyl)oxy]carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid, monosodium salt (0.0274 mmol) is added. The reaction mixture is stirred for 1-2 days, and then concentrated to an oil under high vacuum. The oil is purified by preparative HPLC to obtain the desired product.

Example 23

Synthesis of cyclo{Lys-Gly-Asp-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-Val}, SEQ ID NO: 38--

Please replace the paragraphs on page 177, l. 20 to page 179, l. 17 with the following rewritten paragraphs:

-- Part A: Preparation of cyclo{Lys(Tfa)-Gly-Asp(OBzl)-D-Tyr(N-Cbz-3-aminopropyl)-Val}, SEQ ID NO: 38

The N-terminus Boc- protecting group of the peptide sequence Boc-Asp(OBzl)-D-Tyr(N-Cbz-aminopropyl)-Val-Lys(Tfa)-Gly-Oxime, SEQ ID NO: 39, resin is removed using standard deprotection (25% TFA in CH_2Cl_2). After eight washes with DCM, the resin is treated with 10% DIEA/DCM (2 x 10 min.). The resin is subsequently washed with DCM (x 5) and dried under high vacuum. The resin (1.75 g, 0.55 mmol/g) is then suspended in dimethylformamide (15 mL). Glacial acetic acid (55.0 μL, 0.961 mmol) is added, and the reaction mixture is heated at 50 °C for 72 h. The resin is filtered, and washed with DMF (2 x 10 mL). The filtrate is concentrated to an oil under high vacuum. The resulting oil is triturated with ethyl acetate. The solid thus obtained is filtered, washed with ethyl acetate, and is dried under high vacuum to obtain the desired product.

Part B: Preparation of cyclo{Lys(Tfa)-Gly-Asp-D-Tyr(3-aminopropyl)-Val} Trifluoroacetic acid salt, SEQ ID NO: 38

Cyclo{Lys(Tfa)-Gly-Asp(OBzl)-D-Tyr(N-Cbz-3-aminopropyl)-Val}, SEQ ID NO: 38, (0.146 mmol) is dissolved in trifluoroacetic acid (0.6 mL) and cooled to -10 °C. Trifluoromethanesulfonic acid (0.5 mL) is added dropwise,

maintaining the temperature at -10 °C. Anisole (0.1 mL) is added and the reaction mixture is stirred at -10 °C for 3 h. Diethyl ether is added, the reaction mixture cooled to -35 °C and then stirred for 30 min. The reaction mixture is cooled further to -50 °C and stirred for 30 min. The crude product obtained is filtered, washed with diethyl ether, dried under high vacuum, and is purified by preparative HPLC to obtain the desired product.

Part C. Preparation of cyclo{Lys-Gly-Asp-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-Val}, SEQ ID NO: 38

Cyclo{Lys(Tfa)-Gly-Asp-D-Tyr(3-aminopropyl)-Val}, SEQ ID NO: 38, trifluoroacetic acid salt (0.0228 mmol) is dissolved in DMF (1 mL). Triethylamine (0.0648 mmol) is added, and after 5 min of stirring 2-[[[5-[[(2,5-dioxo-1-pyrrolidinyl)oxy]carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid, monosodium salt (0.0274 mmol) is added. The reaction mixture is stirred for 1-2 days, and then concentrated to an oil under high vacuum. The oil is treated with 20% piperidine in DMF, and the crude material is purified by preparative HPLC to obtain the desired product.

Example 24

Synthesis of cyclo{Cys(2-aminoethyl)-Gly-Asp-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-Val}, SEQ ID NO: 40--

Please replace the paragraphs on page 179, l. 21 to page 181, l. 21 with the following rewritten paragraphs:

--Part A: Preparation of cyclo{Cys(2-N-Tfa-aminoethyl)-Gly-Asp(OBzl)-D-Tyr(N-Cbz-3-aminopropyl)-Val}, SEQ ID NO: 40

The N-terminus Boc- protecting group of the peptide sequence Boc-Asp(OBzl)-D-Tyr(N-Cbz-aminopropyl)-Val-Cys(2-N-Tfa-aminoethyl)-Gly-Oxime, SEQ ID NO: 41, resin is removed using standard deprotection (25% TFA in CH_2Cl_2). After eight washes with DCM, the resin is treated with 10% DIEA/DCM (2 x 10 min.). The resin is subsequently washed with DCM (x 5) and dried under high vacuum. The resin (1.75 g, 0.55 mmol/g) is then suspended in dimethylformamide (15 mL). Glacial acetic acid (55.0 μL, 0.961 mmol) is added, and the reaction mixture is heated at 50 °C for 72 h. The resin is filtered, and washed with DMF (2 x 10 mL). The filtrate is concentrated to an oil under high vacuum. The resulting oil is triturated with ethyl acetate. The solid thus obtained is filtered, washed with ethyl acetate, and dried under high vacuum to obtain the desired product.

Part B: Preparation of cyclo{Cys(2-N-Tfa-aminoethyl)-Gly-Asp-D-Tyr(3-aminopropyl)-Val}, SEQ ID NO: 40, Trifluoroacetic acid salt.

Cyclo{Cys(2-N-Tfa-aminoethyl)-Gly-Asp(OBzl)-D-Tyr(N-Cbz-3-aminopropyl)-Val}, SEQ ID NO: 40, (0.146 mmol) is dissolved in trifluoroacetic acid (0.6 mL) and cooled to -10 °C. Trifluoromethanesulfonic acid (0.5 mL) is added dropwise, maintaining the temperature at -10 °C. Anisole (0.1 mL) is added and the reaction mixture is stirred at -10 °C for 3 h. Diethyl ether is added, the reaction mixture cooled to -35 °C and then stirred for 30 min. The reaction mixture is cooled further to -50 °C and stirred for 30 min. The crude product obtained is filtered, washed with diethyl ether, dried under high vacuum, and is purified by preparative HPLC to obtain the desired product.

Part C. Preparation of cyclo{Cys(2-aminoethyl)-Gly-Asp-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-Val}, SEQ ID NO: 40

Cyclo{Cys(2-N-Tfa-aminoethyl)-Gly-Asp-D-Tyr(3-aminopropyl)-Val}, SEQ ID NO: 40, trifluoroacetic acid salt (0.0228 mmol) is dissolved in DMF (1 mL). Triethylamine (9.5 μL, 0.0648 mmol) is added, and after 5 min of stirring 2-[[[5-[[(2,5-dioxo-1-pyrrolidinyl)oxy]carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid, monosodium salt (0.0121 g, 0.0274 mmol) is added. The reaction mixture is stirred for 1-2 days, and then concentrated to an oil under high vacuum. The oil is treated with 20% piperidine in DMF, and the crude material is purified by preparative HPLC to obtain the desired product.

Example 25

Synthesis of cyclo{HomoLys-Gly-Asp-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-Val}, SEQ ID NO: 38--

Please replace the paragraphs on page 182, l. 1 to page 183, l. 23 with the following rewritten paragraphs:

--Part A: Preparation of cyclo{HomoLys(Tfa)-Gly-Asp(OBzl)-D-Tyr(N-Cbz-3-aminopropyl)-Val}, SEQ ID NO: 38

The N-terminus Boc- protecting group of the peptide sequence Boc-Asp(OBzl)-D-Tyr(N-Cbz-aminopropyl)-Val-HomoLys(Tfa)-Gly-Oxime, SEQ ID NO: 39, resin is removed using standard deprotection (25% TFA in CH_2Cl_2). After eight washes with DCM, the resin is treated with 10% DIEA/DCM (2 x 10 min.). The resin is subsequently washed with DCM (x 5) and dried under high vacuum. The resin (1.75 g, 0.55 mmol/g) is

then suspended in dimethylformamide (15 mL). Glacial acetic acid (55.0 μL, 0.961 mmol) is added, and the reaction mixture is heated at 50 °C for 72 h. The resin is filtered, and washed with DMF (2 x 10 mL). The filtrate is concentrated to an oil under high vacuum. The resulting oil is triturated with ethyl acetate. The solid thus obtained is filtered, washed with ethyl acetate, and dried under high vacuum to obtain the desired product.

Part B: Preparation of cyclo{HomoLys(Tfa)-Gly-Asp-D-Tyr(3-aminopropyl)-Val}, SEQ ID NO: 38, Trifluoroacetic acid salt.

Cyclo{HomoLys(Tfa)-Gly-Asp(OBzl)-D-Tyr(N-Cbz-3-aminopropyl)-Val}, SEQ ID NO: 38, (0.146 mmol) is dissolved in trifluoroacetic acid (0.6 mL) and cooled to -10 °C. Trifluoromethanesulfonic acid (0.5 mL) is added dropwise, maintaining the temperature at -10 °C. Anisole (0.1 mL) is added and the reaction mixture is stirred at -10 °C for 3 h. Diethyl ether is added, the reaction mixture cooled to -35 °C and then stirred for 30 min. The reaction mixture is cooled further to -50 °C and stirred for 30 min. The crude product obtained is filtered, washed with diethyl ether, dried under high vacuum, and is purified by preparative HPLC to obtain the desired product.

Part C. Preparation of cyclo{HomoLys-Gly-Asp-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-Val}, SEQ ID NO: 38

Cyclo{HomoLys(Tfa)-Gly-Asp-D-Tyr(3-aminopropyl)-Val}, SEQ ID NO: 38, trifluoroacetic acid salt (0.0228 mmol) is dissolved in DMF (1 mL). Triethylamine (9.5 μL, 0.0648 mmol) is added, and after 5 min of stirring 2-[[[5-[[(2,5-dioxo-1-

pyrrolidinyl)oxy]carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid, monosodium salt (0.0121 g, 0.0274 mmol) is added. The reaction mixture is stirred for 1-2 days, and then concentrated to an oil under high vacuum. The oil is treated with 20% piperidine in DMF, and the crude material is purified by preparative HPLC to obtain the desired product.

Example 26

Synthesis of cyclo{Orn(d-N-Benzylcarbamoyl)-Gly-Asp-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-Val}, SEQ ID NO: 33--

Please replace the paragraphs on page 184, l. 1 to page 185, l. 26 with the following rewritten paragraphs:

-- Part A: Preparation of cyclo{Orn(d-N-Benzylcarbamoyl)-Gly-Asp(OBzl)-D-Tyr(N-Cbz-3-aminopropyl)-Val}, SEQ ID NO: 33

The N-terminus Boc- protecting group of the peptide sequence Boc-Asp(OBzl)-D-Tyr(N-Cbz-aminopropyl)-Val-Orn(d-N-Benzylcarbamoyl)-Gly-Oxime, SEQ ID NO: 34, resin is removed using standard deprotection (25% TFA in CH_2Cl_2). After eight washes with DCM, the resin is treated with 10% DIEA/DCM (2 x 10 min.). The resin is subsequently washed with DCM (x 5) and dried under high vacuum. The resin (1.75 g, 0.55 mmol/g) is then suspended in dimethylformamide (15 mL). Glacial acetic acid (55.0 μL, 0.961 mmol) is added, and the reaction mixture is heated at 50 °C for 72 h. The resin is filtered, and washed with DMF (2 x 10 mL). The filtrate is concentrated to an oil under high vacuum. The resulting oil is triturated with ethyl acetate. The solid thus obtained is filtered, washed with ethyl acetate, and dried under high vacuum to obtain the desired product.

Part B: Preparation of cyclo{Orn(d-N-Benzylcarbamoyl)-Gly-Asp-D-Tyr(3-aminopropyl)-Val}, SEQ ID NO: 33. Trifluoroacetic acid salt.

Cyclo{Orn(d-N-Benzylcarbamoyl)-Gly-Asp(OBzl)-D-Tyr(N-Cbz-3-aminopropyl)-Val}, SEQ ID NO: 33, (0.146 mmol) is dissolved in trifluoroacetic acid (0.6 mL) and cooled to -10 °C. Trifluoromethanesulfonic acid (0.5 mL) is added dropwise, maintaining the temperature at -10 °C. Anisole (0.1 mL) is added and the reaction mixture is stirred at -10 °C for 3 h. Diethyl ether is added, the reaction mixture cooled to -35 °C and then stirred for 30 min. The reaction mixture is cooled further to -50 °C and stirred for 30 min. The crude product obtained is filtered, washed with diethyl ether, dried under high vacuum, and is purified by preparative HPLC to obtain the desired product.

Part C. Preparation of cyclo{Orn(d-N-Benzylcarbamoyl)-Gly-Asp-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-Val}, SEQ ID NO: 33

Cyclo{Orn(d-N-Benzylcarbamoyl)-Gly-Asp-D-Tyr(3-aminopropyl)-Val}, SEQ ID NO: 33, trifluoroacetic acid salt (0.0228 mmol) is dissolved in DMF (1 mL). Triethylamine (9.5 μL, 0.0648 mmol) is added, and after 5 min of stirring 2-[[[5-[[(2,5-dioxo-1-pyrrolidinyl)oxy]carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid, monosodium salt (0.0121 g, 0.0274 mmol) is added. The reaction mixture is stirred for 1-2 days, and then concentrated to an oil under high vacuum. The oil is purified by preparative HPLC to obtain the desired product.

Example 27

Synthesis of cyclo{Dap(b-(2-benzimidazolylacetyl))-Gly-Asp-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-Val}, SEQ ID NO: 42--

Please replace the paragraphs on page 186, l. 3 to page 188, l. 7 with the following rewritten paragraphs:

-- Part A: Preparation of cyclo{Dap(b-(1-Tos-2-benzimidazolylacetyl))-Gly-Asp(OBzl)-D-Tyr(N-Cbz-3-aminopropyl)-Val}, SEQ ID NO: 42

The N-terminus Boc- protecting group of the peptide sequence Boc-Asp(OBzl)-D-Tyr(N-Cbz-aminopropyl)-Val-Dap(b-(1-Tos-2-benzimidazolylacetyl))-Gly-Oxime, SEQ ID NO: 43, resin is removed using standard deprotection (25% TFA in CH_2Cl_2). After eight washes with DCM, the resin is treated with 10% DIEA/DCM (2 x 10 min.). The resin is subsequently washed with DCM (x 5) and dried under high vacuum. The resin (1.75 g, 0.55 mmol/g) is then suspended in dimethylformamide (15 mL). Glacial acetic acid (55.0 μL, 0.961 mmol) is added, and the reaction mixture is heated at 50 °C for 72 h. The resin is filtered, and washed with DMF (2 x 10 mL). The filtrate is concentrated to an oil under high vacuum. The resulting oil is triturated with ethyl acetate. The solid thus obtained is filtered, washed with ethyl acetate, and dried under high vacuum to obtain the desired product.

Part B: Preparation of cyclo{Dap(b-(2-benzimidazolylacetyl))-Gly-Asp-D-Tyr(3-aminopropyl)-Val}, SEQ ID NO: 42. Trifluoroacetic acid salt.

Cyclo{Dap(b-(1-Tos-2-benzimidazolylacetyl))-Gly-Asp(OBzl)-D-Tyr(N-Cbz-3-aminopropyl)-Val}, SEQ ID NO: 42,

(0.146 mmol) is dissolved in trifluoroacetic acid (0.6 mL) and cooled to -10 °C. Trifluoromethanesulfonic acid (0.5 mL) is added dropwise, maintaining the temperature at -10 °C. Anisole (0.1 mL) is added and the reaction mixture is stirred at -10 °C for 3 h. Diethyl ether is added, the reaction mixture cooled to -35 °C and then stirred for 30 min. The reaction mixture is cooled further to -50 °C and stirred for 30 min. The crude product obtained is filtered, washed with diethyl ether, dried under high vacuum, and purified by preparative HPLC to obtain the desired product.

Part C. Preparation of cyclo{Dap(b-(2-benzimidazolylacetyl))-Gly-Asp-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-Val}, SEQ ID NO: 42

Cyclo{Dap(b-(2-benzimidazolylacetyl))-Gly-Asp-D-Tyr(3-aminopropyl)-Val}, SEQ ID NO: 42, trifluoroacetic acid salt (0.0228 mmol) is dissolved in DMF (1 mL). Triethylamine (9.5 μL, 0.0648 mmol) is added, and after 5 min of stirring 2-[[[5-[[(2,5-dioxo-1-pyrrolidinyl)oxy]carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid, monosodium salt (0.0121 g, 0.0274 mmol) is added. The reaction mixture is stirred for 1-2 days, and then concentrated to an oil under high vacuum. The oil is purified by the method described below to obtain the desired product.

Example 28

Synthesis of cyclo{Orn(d-N-2-Imidazolinyl)-Gly-Asp-D-Phe-Lys(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])}, SEQ ID NO: 35--

Please replace the paragraphs on page 188, l. 11 to page 190, l. 7 with the following rewritten paragraphs:

-- Part A: Preparation of cyclo{Orn(d-N-1-Tos-2-Imidazolinyl)-Gly-Asp(OBzl)-D-Phe-Lys(Cbz)}, SEQ ID NO: 35

The N-terminus Boc- protecting group of the peptide sequence Boc-Asp(OBzl)-D-Phe-Lys(Z)-Orn(d-N-1-Tos-2-Imidazolinyl)-Gly-Oxime, SEQ ID NO: 36, resin is removed using standard deprotection (25% TFA in CH_2Cl_2). After eight washes with DCM, the resin is treated with 10% DIEA/DCM (2 x 10 min.). The resin is subsequently washed with DCM (x 5) and dried under high vacuum. The resin (1.75 g, 0.55 mmol/g) is then suspended in dimethylformamide (15 mL). Glacial acetic acid (55.0 μL, 0.961 mmol) is added, and the reaction mixture is heated at 50 °C for 72 h. The resin is filtered, and washed with DMF (2 x 10 mL). The filtrate is concentrated to an oil under high vacuum. The resulting oil is triturated with ethyl acetate. The solid thus obtained is filtered, washed with ethyl acetate, and dried under high vacuum to obtain the desired product.

Part B. Preparation of cyclo{Orn(d-N-2-Imidazolinyl)-Gly-Asp-D-Phe-Lys}, SEQ ID NO: 35

Cyclo{Orn(d-N-1-Tos-2-Imidazolinyl)-Gly-Asp(OBzl)-D-Phe-Lys(Cbz)}, SEQ ID NO: 35, (0.204 mmol) is dissolved in trifluoroacetic acid (0.6 mL) and cooled to -10 °C. Trifluoromethanesulfonic acid (0.5 mL) is added dropwise, maintaining the temperature at -10 °C. Anisole (0.1 mL) is added and the reaction is stirred at -10 °C for 3 h. Diethyl ether is added, the reaction is cooled to -50 °C, and stirred for 1 h. The crude product is filtered, washed with diethyl

ether, dried under high vacuum and purified by preparative HPLC to obtain the desires product.

Part C. Preparation of cyclo{Orn(d-N-2-Imidazolinyl)-Gly-Asp-D-Phe-Lys(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])}, SEQ ID NO: 35

Cyclo{Orn(d-N-2-Imidazolinyl)-Gly-Asp-D-Phe-Lys}, SEQ ID NO: 35, TFA salt (0.0481 mmol) is dissolved in DMF (2 mL). Triethylamine (20.1 μL, 0.144 mmol) is added, and after 5 min of stirring 2-[[[5-[[(2,5-dioxo-1-pyrrolidinyl)oxy]carbonyl]-2-pyridinyl]hydrazono]-methyl]-benzenesulfonic acid, monosodium salt (0.0254 g, 0.0577 mmol) is added. The reaction mixture is stirred for 20 h and then concentrated to an oil under high vacuum. The oil is purified by preparative HPLC to obtain the desired product.

Example 29

Synthesis of cyclo{Orn(d-N-Benzylcarbamoyl)-Gly-Asp-D-Phe-Lys(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])}, SEQ ID NO: 35--

Please replace the paragraphs on page 190, l. 11 to page 192, l. 7 with the following rewritten paragraphs:

-- Part A: Preparation of cyclo{Orn(d-N-Benzylcarbamoyl)-Gly-Asp(OBzl)-D-Phe-Lys(Cbz)}, SEQ ID NO: 35

The N-terminus Boc- protecting group of the peptide sequence Boc-Asp(OBzl)-D-Phe-Lys(Z)-Orn(d-N-Benzylcarbamoyl)-Gly-Oxime, SEQ ID NO: 36, resin is removed using standard deprotection (25% TFA in CH_2Cl_2). After eight washes with DCM, the resin is treated with 10% DIEA/DCM (2 x 10 min.). The resin is subsequently washed with DCM (x 5) and dried

under high vacuum. The resin (1.75 g, 0.55 mmol/g) is then suspended in dimethylformamide (15 mL). Glacial acetic acid (55.0 μL, 0.961 mmol) is added, and the reaction mixture is heated at 50 °C for 72 h. The resin is filtered, and washed with DMF (2 x 10 mL). The filtrate is concentrated to an oil under high vacuum. The resulting oil is triturated with ethyl acetate. The solid thus obtained is filtered, washed with ethyl acetate, and dried under high vacuum to obtain the desired product.

Part B. Preparation of cyclo{Orn(d-N-Benzylcarbamoyl)-Gly-Asp-D-Phe-Lys}, SEQ ID NO: 35

Cyclo{Orn(d-N-Benzylcarbamoyl)-Gly-Asp(OBzl)-D-Phe-Lys(Cbz)}, SEQ ID NO: 35, (0.204 mmol) is dissolved in trifluoroacetic acid (0.6 mL) and cooled to -10 °C. Trifluoromethanesulfonic acid (0.5 mL) is added dropwise, maintaining the temperature at -10 °C. Anisole (0.1 mL) is added and the reaction is stirred at -10 °C for 3 h. Diethyl ether is added, the reaction is cooled to -50 °C, and stirred for 1 h. The crude product is filtered, washed with diethyl ether, dried under high vacuum and purified by preparative HPLC to obtain the desires product.

Part C. Preparation of cyclo{Orn(d-N-Benzylcarbamoyl)-Gly-Asp-D-Phe-Lys(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])}, SEQ ID NO: 35

Cyclo{Orn(d-N-Benzylcarbamoyl)-Gly-Asp-D-Phe-Lys}, SEQ ID NO: 35, TFA salt (0.0481 mmol) is dissolved in DMF (2 mL). Triethylamine (20.1 μL, 0.144 mmol) is added, and after 5 min of stirring 2-[[[5-[[(2,5-dioxo-1-pyrrolidinyl)oxy]carbonyl]-

2-pyridinyl]hydrazono]-methyl]-benzenesulfonic acid, monosodium salt (0.0254 g, 0.0577 mmol) is added. The reaction mixture is stirred for 20 h and then concentrated to an oil under high vacuum. The oil is purified by preparative HPLC to obtain the desired product.

Example 30

Synthesis of cyclo{Lys-D-Val-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-D-Asp-Gly}, SEQ ID NO: 44--

Please replace the paragraphs on page 192, l. 11 to page 194, l. 5 with the following rewritten paragraphs:

-- Part A: Preparation of cyclo{Lys(Tfa)-D-Val-D-Tyr(N-Cbz-3-aminopropyl)-D-Asp(OBzl)-Gly}, SEQ ID NO: 44

The N-terminus Boc-protecting group of the peptide sequence Boc-Lys(Tfa)-D-Val-D-Tyr(N-Cbz-aminopropyl)-D-Asp(OBzl)-Gly-Oxime, SEQ ID NO: 44, resin is removed using standard deprotection (50% TFA in CH_2Cl_2). After washing with DCM (8x), the resin is neutralized with 10% DIEA/DCM (2 x 10 min). The resin is washed with DCM (5x) and dried under high vacuum overnight. The resin (1.0 g, about 0.36 mmol/g) is then suspended in N,N-dimethylformamide (12 mL). Glacial acetic acid (67 mL, 1.16 mmol) is added and the reaction mixture is heated to 55 ^{o}C for 72 h. The resin is filtered and washed with DMF (3 x 10 mL). The filtrate is concentrated under high vacuum to give an oil. The resulting oil is triturated with ethyl acetate. The desired product is purified by reverse-phase HPLC.

Part B: Preparation of cyclo{Lys-D-Val-D-Tyr(3-aminopropyl)-D-Asp-Gly}, SEQ ID NO: 44, Trifuoroacetic acid salt.

The protected cyclic peptide cyclo{Lys(Tfa)-D-Val-D-Tyr(N-Cbz-3-aminopropyl)-D-Asp(OBzl)-Gly}, SEQ ID NO: 44, (0.10 mmol) is dissolved in trifluoroacetic acid (0.95 mL) and cooled to -10 °C in a dry ice/acetone bath. To this solution is added trifluoromethanesulfonic acid (0.12 mmol), followed by anisole (190 mL). The reaction mixture is stirred at -16 °C for 3 h. The dry ice/acetone bath is then cooled to -35 °C and cold ether (40 mL) is added to the solution. The mixture is stirred for 30 min at -35 °C, then cooled to -50 °C and stirred for another 30 min. The crude product is filtered, redissolved in water/acetonitrile (1/1), lyophilized, and purified by reverse-phase HPLC to give the desired product.

Part C: Preparation of cyclo{Lys-D-Val-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-D-Asp-Gly}, SEQ ID NO: 44

A solution of cyclo{Lys(Tfa)-D-Val-D-Tyr(3-aminopropyl)-D-Asp-Gly}, SEQ ID NO: 44, (0.0216 mmol) in N,N-dimethylformamide (2 mL) is added triethylamine (15 mL, 0.108 mmol) and stirred at room temperature for 10 min. 2-[[[5-[[(2,5-Dioxo-1-pyrrolidinyl)oxy]carbonyl-2-pyridinyl]-hydrazono]methyl-benzenesulfonic acid, monosodium salt (0.0260 mmol) is added, and the mixture is stirred for 18 h. The mixture is concentrated under high vacumm, the oil is treated with 20% piperidine in DMF, and is again concntrated in vacuo. The residue is purified by reverse-phase HPLC to give the desired product.

Example 31

Synthesis of cyclo{Orn(d-N-Benzylcarbamoyl)-D-Val-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-D-Asp-Gly}, SEQ ID NO: 37--

Please replace the paragraphs on page 194, l. 9 to page 196, l. 7 with the following rewritten paragraphs:

-- Part A: Preparation of cyclo{Orn(d-N-Benzylcarbamoyl)-D-Val-D-Tyr(N-Cbz-3-aminopropyl)-D-Asp(OBzl)-Gly}, SEQ ID NO: 37

The N-terminus Boc-protecting group of the peptide sequence Boc-Orn(d-N-Benzylcarbamoyl)-D-Val-D-Tyr(N-Cbz-aminopropyl)-D-Asp(OBzl)-Gly-Oxime, SEQ ID NO: 37, resin is removed using standard deprotection (50% TFA in CH_2Cl_2). After washing with DCM (8x), the resin is neutralized with 10% DIEA/DCM (2 x 10 min). The resin is washed with DCM (5x) and dried under high vacuum overnight. The resin (1.0 g, about 0.36 mmol/g) is then suspended in N,N-dimethylformamide (12 mL). Glacial acetic acid (67 mL, 1.16 mmol) is added and the reaction mixture is heated to 55 °C for 72 h. The resin is filtered and washed with DMF (3 x 10 mL). The filtrate is concentrated under high vacuum to give an oil. The resulting oil is triturated with ethyl acetate. The desired product is purified by reverse-phase HPLC.

Part B: Preparation of cyclo{Orn(d-N-Benzylcarbamoyl)-D-Val-D-Tyr(3-aminopropyl)-D-Asp-Gly}, SEQ ID NO: 37, Trifuoroacetic acid salt.

The protected cyclic peptide cyclo{Orn(d-N-Benzylcarbamoyl)-D-Val-D-Tyr(N-Cbz-3-aminopropyl)-D-Asp(OBzl)-Gly}, SEQ ID NO: 37, (0.10 mmol) is dissolved in trifluoroacetic acid (0.95 mL) and cooled to -10 °C in a dry ice/acetone bath. To this solution is added trifluoromethanesulfonic acid (0.12 mmol), followed by anisole (190 mL). The reaction mixture is stirred at -16 °C for 3 h. The dry ice/acetone bath is then cooled to -35 °C and cold ether (40 mL) is added to the solution. The mixture

is stirred for 30 min at -35 °C, then cooled to -50 °C and stirred for another 30 min. The crude product is filtered, redissolved in water/acetonitrile (1/1), lyophilized, and purified by reverse-phase HPLC to give the desired product.

Part C: Preparation of cyclo{Orn(d-N-Benzylcarbamoyl)-D-Val-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-D-Asp-Gly}, SEQ ID NO: 37

A solution of cyclo{Orn(d-N-Benzylcarbamoyl)-D-Val-D-Tyr(3-aminopropyl)-D-Asp-Gly}, SEQ ID NO: 37, (0.0216 mmol) in N,N-dimethylformamide (2 mL) is added triethylamine (15 mL, 0.108 mmol) and stirred at room temperature for 10 min. 2-[[[5-[[(2,5-Dioxo-1-pyrrolidinyl)oxy]carbonyl-2-pyridinyl]-hydrazono]methyl-benzenesulfonic acid, monosodium salt (0.0260 mmol) is added, and the mixture is stirred for 18 h. The mixture is concentrated under high vacumm and the residue is purified by reverse-phase HPLC to give the desired product.

Example 32

Synthesis of cyclo{Orn(d-N-2-Imidazolinyl)-D-Val-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-D-Asp-Gly}, SEQ ID NO: 37--

Please replace the paragraphs on page 196, l. 11 to page 198, l. 28 with the following rewritten paragraphs:

-- Part A: Preparation of cyclo{Orn(d-N-1-Tos-2-Imidazolinyl)-D-Val-D-Tyr(N-Cbz-3-aminopropyl)-D-Asp(OBzl)-Gly}, SEQ ID NO: 37

The N-terminus Boc-protecting group of the peptide sequence Boc-Orn(d-N-1-Tos-2-Imidazolinyl)-D-Val-D-Tyr(N-Cbz-aminopropyl)-D-Asp(OBzl)-Gly-Oxime, SEQ ID NO: 37, resin is

removed using standard deprotection (50% TFA in CH_2Cl_2). After washing with DCM (8x), the resin is neutralized with 10% DIEA/DCM (2 x 10 min). The resin is washed with DCM (5x) and dried under high vacuum overnight. The resin (1.0 g, about 0.36 mmol/g) is then suspended in N,N-dimethylformamide (12 mL). Glacial acetic acid (67 mL, 1.16 mmol) is added and the reaction mixture is heated to 55 °C for 72 h. The resin is filtered and washed with DMF (3 x 10 mL). The filtrate is concentrated under high vacuum to give an oil. The resulting oil is triturated with ethyl acetate. The desired product is purified by reverse-phase HPLC.

Part B: Preparation of cyclo{Orn(d-N-2-Imidazolinyl)-D-Val-D-Tyr(3-aminopropyl)-D-Asp-Gly}, SEQ ID NO: 37, Trifuoroacetic acid salt.

The protected cyclic peptide cyclo{Orn(d-N-1-Tos-2-Imidazolinyl)-D-Val-D-Tyr(N-Cbz-3-aminopropyl)-D-Asp(OBzl)-Gly}, SEQ ID NO: 37, (0.10 mmol) is dissolved in trifluoroacetic acid (0.95 mL) and cooled to -10 °C in a dry ice/acetone bath. To this solution is added trifluoromethanesulfonic acid (0.12 mmol), followed by anisole (190 mL). The reaction mixture is stirred at -16 °C for 3 h. The dry ice/acetone bath is then cooled to -35 °C and cold ether (40 mL) is added to the solution. The mixture is stirred for 30 min at -35 °C, then cooled to -50 °C and stirred for another 30 min. The crude product is filtered, redissolved in water/acetonitrile (1/1), lyophilized, and purified by reverse-phase HPLC to give the desired product.

Part C: Preparation of cyclo{Orn(d-N-2-Imidazolinyl)-D-Val-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-D-Asp-Gly}, SEQ ID NO: 37

A solution of cyclo{Orn(d-N-2-Imidazolinyl)-D-Val-D-Tyr(3-aminopropyl)-D-Asp-Gly}, SEQ ID NO: 37, (0.0216 mmol) in N,N-dimethylformamide (2 mL) is added triethylamine (15 mL, 0.108 mmol) and stirred at room temperature for 10 min. 2-[[[5-[[(2,5-Dioxo-1-pyrrolidinyl)oxy]carbonyl-2-pyridinyl]-hydrazono]methyl-benzenesulfonic acid, monosodium salt (0.0260 mmol) is added, and the mixture is stirred for 18 h. The mixture is concentrated under high vacumm and the residue is purified by reverse-phase HPLC to give the desired product.--

Please replace the paragraph on page 207, l. 2-4 with the following rewritten paragraph:

--Part A. Synthesis of 1-(1,2-Dipalmitoyl-sn-glycero-3-phosphoethanolamino)-12-(cyclo(Arg-Gly-Asp-D-Phe-Lys)-dodecane-1,12-dione, SEQ ID NO: 3--

Please replace the paragraphs on page 207, l. 9 to page 208, l. 13 with the following rewritten paragraphs:

--A solution of disuccinimidyl dodecane-1,12-dioate (0.424 g, 1 mmol), 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine (1.489 g, 1 mmol) and cyclo(Arg-Gly-Asp-D-Phe-Lys), SEQ ID NO: 3, TFA salt (0.831 g, 1 mmol) in 25 ml chloroform is stirred for 5 min. Sodium carbonate (1 mmol) and sodium sulfate (1 mmol) are added and the solution is stirred at room temperature under nitrogen for 18 h. DMF is removed in vacuo and the crude product is purified to obtain the title compound.

Part B. Preparation of Contrast Agent Composition

The Synthesis of 1-(1,2-Dipalmitoyl-sn-glycero-3-phosphoethanolamino)-12-(cyclo(Arg-Gly-Asp-D-Phe-Lys)-dodecane-1,12-dione, SEQ ID NO: 3, is admixed with three other

lipids, 1,2-dipalmitoyl-sn-glycero-3-phosphotidic acid, 1,2-dipalmitoyl-sn-glycero-3-phosphatidylcholine, and N-(methoxypolyethylene glycol 5000 carbamoyl)-1,2-dipalmitoyl-sn-glycero-3-phosphatidylethanolamine in relative amounts of 1 wt.%:6 wt.%:54 wt.%:41 wt.%. An aqueous solution of this lipid admixture (1 mg/mL), sodium chloride (7 mg/mL), glycerin (0.1 mL/mL), propylene glycol (0.1 mL/mL), at pH 6-7 is then prepared in a 2 cc glass vial. The air in the vial is evacuated and replaced with perfluoropropane and the vial is sealed. The ultrasound contrast agent composition is completed by agitating the sealed vial in a dental amalgamator for 30-45 sec. to form a milky white solution.

Example 65

Part A. Preparation of (ω-amino-PEG_{3400}-α-carbonyl)-cyclo(Arg-Gly-Asp-D-Phe-Lys), SEQ ID NO: 3--

Please replace the paragraphs on page 208, l. 16 to page 209, l. 3 with the following rewritten paragraphs:

--To a solution of N-Boc-ω-amino-PEG_{3400}-α-carboxylate sucinimidyl ester (1 mmol) and cyclo(Arg-Gly-Asp-D-Phe-Lys), SEQ ID NO: 3, (1 mmol) in DMF (25 mL) is added triethylamine (3 mmol). The reaction mixture is stirred under nitrogen at room temperature overnight and the solvent is removed in vacuo. The crude product is dissolved in 50% trifluoroacetic acid/dichloromethane and is stirred for 4 h. The volatiles are removed and the title compound is isolated as the TFA salt via trituration in diethyl ether.

Part B. Preparation of 1-(1,2-Dipalmitoyl-sn-glycero-3-phosphoethanolamino)-12-((ω-amino-PEG_{3400}-α-carbonyl)-cyclo(Arg-Gly-Asp-D-Phe-Lys))-Dodecane-1,12-Dione, SEQ ID NO: 3--

Please replace the paragraphs on page 209, l. 6 to page 210, l. 12 with the following rewritten paragraphs:

-- A solution of disuccinimidyl dodecanoate (1 mmol), 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine (1 mmol) and (ω-amino-PEG_{3400}-α-carbonyl)-cyclo(Arg-Gly-Asp-D-Phe-Lys), SEQ ID NO: 3, TFA salt (1 mmol) in 25 ml chloroform is stirred for 5 min. Sodium carbonate (1 mmol) and sodium sulfate (1 mmol) are added and the solution is stirred at room temperature under nitrogen for 18 h. DMF is removed in vacuo and the crude product is purified to obtain the title compound.

Part C. Preparation of Contrast Agent Composition

The 1-(1,2-Dipalmitoyl-sn-glycero-3-phosphoethanolamino)-12-((ω-amino-PEG_{3400}-α-carbonyl)-cyclo(Arg-Gly-Asp-D-Phe-Lys))-Dodecane-1,12-Dione, SEQ ID NO:3, is admixed with three other lipids, 1,2-dipalmitoyl-sn-glycero-3-phosphotidic acid, 1,2-dipalmitoyl-sn-glycero-3-phosphatidylcholine, and N-(methoxypolyethylene glycol 5000 carbamoyl)-1,2-dipalmitoyl-sn-glycero-3-phosphatidylethanolamine in relative amounts of 1 wt.%:6 wt.%:54 wt.%:41 wt.%. An aqueous solution of this lipid admixture (1 mg/mL), sodium chloride (7 mg/mL), glycerin (0.1 mL/mL), propylene glycol (0.1 mL/mL), at pH 6-7 is then prepared in a 2 cc glass vial. The air in the vial is evacuated and replaced with perfluoropropane and the vial is sealed. The ultrasound contrast agent composition is completed by agitating the sealed vial in a dental amalgamator for 30-45 sec. to form a milky white solution.

Example 66

Part A. Preparation of Synthesis of (ω-amino-PEG_{3400}-α-carbonyl)-Glu-(cyclo(Arg-Gly-Asp-D-Phe-Lys))$_2$, SEQ ID NO: 16--

Please replace the paragraphs on page 210, l. 16 to page 211, l. 7 with the following rewritten paragraphs:

-- To a solution of N-Boc-ω-amino-PEG_{3400}-α-carboxylate sucinimidyl ester (1 mmol) and Glu-(cyclo(Arg-Gly-Asp-D-Phe-Lys))$_2$, SEQ ID NO: 16, (1 mmol) in DMF (25 mL) is added triethylamine (3 mmol). The reaction mixture is stirred under nitrogen at room temperature overnight and the solvent is removed in vacuo. The crude product is dissolved in 50% trifluoroacetic acid/dichloromethane and is stirred for 4 h. The volatiles are removed and the title compound is isolated as the TFA salt via trituration in diethyl ether.

Part B. Preparation of 1-(1,2-Dipalmitoyl-sn-glycero-3-phosphoethanolamino)-12-((ω-amino-PEG_{3400}-α-carbonyl)-Glu-(cyclo(Arg-Gly-Asp-D-Phe-Lys))$_2$)-Dodecane-1,12-Dione, SEQ ID NO: 16--

Please replace the paragraphs on page 211, l. 11 to page 212, l. 18 with the following rewritten paragraphs:

-- A solution of disuccinimidyl dodecanoate (1 mmol), 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine (1 mmol) and (ω-amino-PEG_{3400}-α-carbonyl)-Glu-(cyclo(Arg-Gly-Asp-D-Phe-Lys))$_2$, SEQ ID NO: 16, TFA salt (1 mmol) in 25 ml chloroform is stirred for 5 min. Sodium carbonate (1 mmol) and sodium sulfate (1 mmol) are added and the solution is stirred at room temperature under nitrogen for 18 h. DMF is removed in vacuo and the crude product is purified to obtain the title compound.

Part C. Preparation of Contrast Agent Composition

The 1-(1,2-Dipalmitoyl-sn-glycero-3-phosphoethanolamino)-12-((ω-amino-PEG_{3400}-α-carbonyl)-Glu-(cyclo(Arg-Gly-Asp-D-Phe-Lys))$_2$)-Dodecane-1,12-Dione, SEQ ID NO:16, is admixed with three other lipids, 1,2-dipalmitoyl-sn-glycero-3-phosphotidic acid, 1,2-dipalmitoyl-sn-glycero-3-phosphatidylcholine, and N-(methoxypolyethylene glycol 5000 carbamoyl)-1,2-dipalmitoyl-sn-glycero-3-phosphatidylethanolamine in relative amounts of 1 wt.%:6 wt.%:54 wt.%:41 wt.%. An aqueous solution of this lipid admixture (1 mg/mL), sodium chloride (7 mg/mL), glycerin (0.1 mL/mL), propylene glycol (0.1 mL/mL), at pH 6-7 is then prepared in a 2 cc glass vial. The air in the vial is evacuated and replaced with perfluoropropane and the vial is sealed. The ultrasound contrast agent composition is completed by agitating the sealed vial in a dental amalgamator for 30-45 sec. to form a milky white solution.--